

New LEA & FEBIGER Books

NEW WORK

JUST READY

DIETETICS FOR THE CLINICIAN

By MILTON ARLANDEN BRIDGES, B S, M D, F A C P.

Associate in Medicine at the New York Post-Graduate Medical School, Columbia Univ., New York

In collaboration with RUTH LOTHROP GALLUP, *Dietitian*. With a foreword by HERMAN O.

MOSENTHAL, A B, M.D., Director of Medicine at the New York Post-Graduate Medical School, Columbia University, New York

Octavo, 666 pages. Cloth, \$6.50, net

This book is designed to fill the great need for a work on dietary management which is readily understandable and from which practice can be immediately instituted. It is written for the general practitioner and the hospital interne, and it should commend itself to the dietetic department of every hospital and clinic. It is a handbook for the worker in the field of medicine who does not have the more detailed treatises at his immediate disposal. The author has reviewed the entire literature of the field at large and has produced an assimilation of the various dietetic tables. The material here offered is not only physiologically sound and essentially practical, but has been adjusted to the physician and his patient.

NEW WORK

JUST READY

INTERNAL MEDICINE

ITS THEORY AND PRACTICE

In Contributions by American Authors

Edited by JOHN H. MUSSER, B S., M.D., F.A.C.P.

Professor of Medicine in The Tulane University of Louisiana School of Medicine; Senior

Visiting Physician to the Charity Hospital, New Orleans, Louisiana

Octavo, 1316 pages, illustrated. Cloth, \$10.00, net

This book is the work of twenty-seven recognized authorities, each of whom holds a professorial appointment in a prominent medical school. Each covers that sub-division of internal medicine in which he is particularly qualified, each writes from the viewpoint of his experience as a teacher and presents his specialized knowledge in such a way as to make the work an authoritative source of information to the student. The book is well organized, without repetitions, concise but comprehensive.

NEW WORK

JUST READY

DIABETES

IN CHILDHOOD AND ADOLESCENCE

By PRISCILLA WHITE, M D, F A C P.

Physician at the New England Deaconess Hospital, Boston, Massachusetts

With a Foreword by ELLIOTT P. JOSLIN, M.D., F.A.C.P.

Octavo, 236 pages, with 25 illustrations and a colored plate. Cloth, \$3.75, net

The living diabetic child is a new phenomenon. Today such children not only survive but become economically independent and the parents of healthy offspring. This book records the conquest of coma and arteriosclerosis in diabetic children. It emphasizes the importance of heredity in diabetes and substantiates its conclusions with striking data. It reports an unusual and valuable experience in caring for Dr. Joslin's younger patients in sickness and health, through childhood and adolescence, and it throws new light on the treatment not only of children but of adult diabetics as well.

LEA & FEBIGER

600 Washington Square
PHILADELPHIA

Please send me books checked:

☐ Bridges - - - - - \$ 6.50
☐ Musser - - - - - 10.00

☐ White - - - - - \$3.75
☐ New Catalogue

Name

Address

(A-1131-33)

ON, MAY

MACMILLAN

MACMILLAN

MACMILLAN

ARTERIOSCLEROSIS

A SURVEY OF
THE PROBLEM

A Publication of the
JOSIAH MACY, JR
FOUNDATION

Edited by

E. V. COWDRY
Washington University, St. Louis



Price
\$5 00

With the pulication of this distinguished volume, the doubts and confusion of years have been set aside

International in scope, searching in its treatment every aspect of the subject has been covered

Contributors

N ANITSCHKOW
LUDWIG ASCHOFF
E T BELL
DANIEL BLAIN
CRIGHTON BRAMWELL
STANLEY COBB
ALFRED E COHN
E. V. COWDRY
HERBERT FOX
JONAS S FRIEDENWALD
HOWARD T KARSNER
FRITZ LANGE
ESMOND R. LONG
W G MACCALLUM
GEORGE R MINOT
WILLIAM OPHULS
A POLICARD
PERCY STOCKS
EDGAR SYDENSTRICKER
SOMA WEISS
H. GIDEON WELLS
GEORGE DEE WILLIAMS
HEN H WICKOFF

Comment

"It can be said with confidence that this volume constitutes the most complete, the most authoritative, and the most illuminating and outstanding contribution to the study of Arteriosclerosis yet made. Student, investigator, pathologist, physician at large—all can read it with profit. Without doubt it will remain an outstanding reference work for some time to come."

—*Jl of Laboratory and Clinical Medicine*

Contents

- | | |
|--|---|
| Introduction | XI Chemistry of Arteriosclerosis |
| I Development of our Knowledge of Arteriosclerosis | XII Acute and Chronic Infections as Etiological Factors |
| II Structure and Physiology of the Blood Vessels | XIII Retinal Arteriosclerosis |
| III Physical Properties of Arteries in Health and Disease | XIV Arteriosclerosis of the Brain and Spinal Cord |
| IV Mineral Constituent of Blood Vessels as Determined by the Technique of Coordination | XV Coronary Arteriosclerosis |
| V Statistical Study of Arteriosclerosis | XVI Sclerosis of the Pulmonary Arteries |
| VI Arteriosclerosis in Lower Mammals and Birds | XVII Arteriosclerosis of the Abdominal Viscera and Extremities |
| VII Race and Climate as Possible Factors | XVIII Hypertension in Relation to Arteriosclerosis |
| VIII Nutrition in Relation to Arteriosclerosis | XIX Hereditary Aspects of Arterial Hypertension in Relation to Arteriosclerosis |
| IX Pathogenesis of Arteriosclerosis | XX Treatment of Arteriosclerosis |
| X Experimental Arteriosclerosis in Animals | XXI Summary |

THE MACMILLAN COMPANY

NEW

NEW YORK

Please Mention this Journal when writing to Advertisers

In congestive heart failure

Theocalcin

(theobromine-calcium salicylate)

Council Accepted



Myocardial stimulation
and a potent diuretic
effect is obtained with
1 to 3 tablets t. i. d.

Tablets $7\frac{1}{2}$ grains each,
also Theocalcin powder.

Literature and samples upon request.

BILHUBER-KNOLL CORP., 154 Ogden Ave., Jersey City, N. J.

*...There is a reason why
Pil. Digitalis (Davies,
Rose) have become the
choice of Cardiologists*

They are digitalis in its completeness—physiologically tested leaves in the form of physiologically standardized pills, giving double assurance of dependability.

Each pill contains 0.1 gram, the equivalent of about $1\frac{1}{2}$ grains of the leaf, or 15 minims of the tincture.

Convenient, uniform, and more accurate than tincture drops.

Sample and literature upon request.

DAVIES, ROSE & CO., Ltd.

Pharmaceutical Manufacturers.



Devitt's Camp, Inc.

ALLENWOOD
PENNSYLVANIA

(Tuberculosis)

*On beautiful White Deer Mountain, 20 miles southeast
of Williamsport, Pa.*

All modern methods of treatment, including heliotherapy, artificial pneumothorax, phrenic exaeresis, Jacobaeus operation, and thoracoplasty

Not operated for profit Moderate rates Modern buildings

Patients given individual attention by experienced physicians and specially trained registered nurses

The following physicians will be glad to examine patients for admittance to Camp

J M ANDERS, M D, Philadelphia, Pa
ISABEL M BALPH, M D, Philadelphia, Pa
E J G BEARDSLEY, M D, Philadelphia, Pa
WARD BRINTON, M D, Philadelphia, Pa
F W J BURGE, M D, Philadelphia, Pa
DONALD R FERGUSON, M D, Philadelphia, Pa

JOHN B FLICK, M D, Philadelphia, Pa
JOHN A KOLMER, M D, Philadelphia, Pa
W ESTELL LEE, M D, Philadelphia, Pa
A C MORGAN, M D, Philadelphia, Pa
GEO MORRIS PIERSOL, M D, Philadelphia, Pa

EDWARD R SNADER, JR, M D, Philadelphia, Pa

MERVYN R TAYLOR, M D, Philadelphia, Pa
THOS J VISCHER, M D, Philadelphia, Pa
A S KECH, M D, Altoona, Pa

CHARLES C HABLSTON, M D, Baltimore, Md

CHARLES S AITKEN, M D, Brookline, Pa

J C ATWELL, M D, Butler, Pa

F DECARIO, M D, Bradford, Pa

J W WOOD, M D, Chester, Pa

JOHN E FRFTZ, M D, Easton, Pa

RICHARD R DALRYMPLE, M D, Erie, Pa
JESSF L LUNKER, M D, Harrisburg, Pa
H B ANDERSON, M D, Johnstown, Pa
JOHN H ESBENSHADE, M D, Lancaster, Pa
E J WERLE, M D, Meadville, Pa
CHARLES G CRANE, M D, Newark, N J
W A WOMER, M D, New Castle, Pa
EDWARD S MCSWEENEY, M D, New York City

M THERESA SCANLAN, M D, New York City

STANLEY L WANG, M D, New York City
W R GLENNEY, M D, Pottsville, Pa

R. R JONES, M D, Pittsburgh, Pa

C L PALMER, M D, Pittsburgh, Pa

A H COLWELL, M D, Pittsburgh, Pa

HOWARD U MILLER, M D, Reading, Pa

A E DAVIS, M D, Scranton, Pa

H D WILLIAMS, M D, Trenton, N J

B M ALLEN, M D, Wilmington, Del

JOHN MINOR, M D, Washington, D C

J W PEABODY, M D, Washington, D C

H R SCHREIBER, M D, Washington, D C

E W BIVBY, M D, Wilkes Barre, Pa

HARRY M READ, M D, York, Pa

BOOKLET

ROSS K CHILDERHOSE, M D

JOHN S PACKARD, M D

Associate Physicians

WILLIAM DEVITT, M D

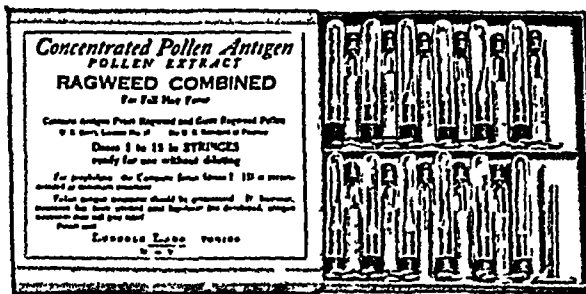
*Superintendent and
Physician in Charge*

Nineteen Years Success with HAY FEVER

In 1914

Our researches resulted in the perfection of Glycerolated Pollen Antigens in stable and standardized solutions. Thus was made available to the general practitioner a means for the scientific treatment of his Hay Fever patients.

Each year has added evidence to the value of these solutions in the prevention and relief from symptoms of Hay Fever and each year an increasing number of physicians have familiarized themselves with the Hay Fever problem and are relieving their patients' seasonal attacks.



Ragweed Combined Antigen Lederle

is supplied in packages of fifteen graduated doses in syringes ready for use without diluting, at \$15 00 Ragweed Combined Antigen, as well as antigens of 49 individual wind borne pollens are available in packages of fifteen graduated doses in vials, with diluting fluid, at \$12 00

90% of the Fall Hay Fever East of the Rocky Mountains from August first to frost is caused by the ragweed pollens. Attacks are greatly relieved or completely controlled through the employment of

Pollen Antigen *Lederle* RAGWEED COMBINED

The LEDERLE LABORATORIES maintain a Department of Allergy supervised by experts and welcome correspondence or visits pertaining to the fever in any locality

LEDERLE LABORATORIES, INC.
511 Fifth Avenue New York

WHY

WYETH'S CAPSULES DIGITALIS LEAF

(DEFATTED)

ARE STANDARDIZED BY
BOTH CAT AND
FROG METHODS



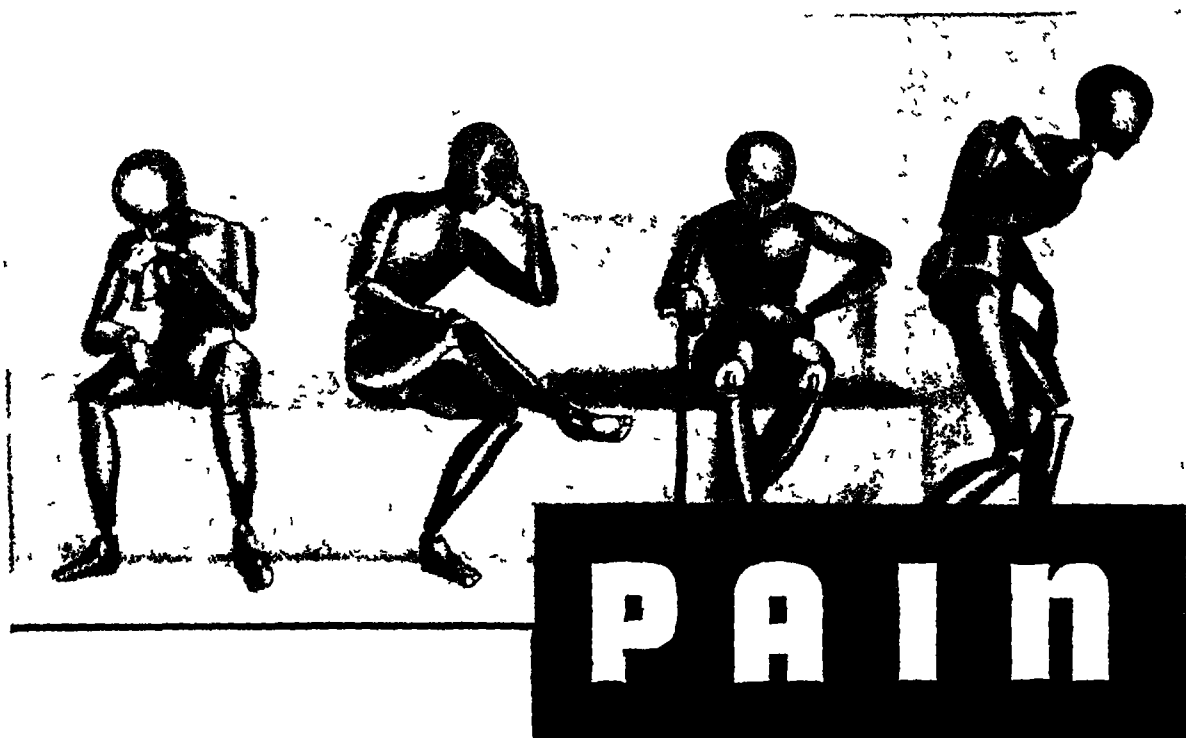
"The U S P directs standardization by the 'one-hour frog-method,' i.e., by the quantity required to produce systolic arrest of the heart in intact frogs, in one hour under standard conditions. Several other frog-methods have also been used. The 'intravenous cat-method' of Hatcher and Brody, 1910, which determines the acutely fatal dose, gives more precise results, but takes no account of absorption. The frog-methods also fail to reproduce clinical absorption, but when the activity with frogs and cats is fairly parallel, the absorption may be considered as normal, whilst wide divergence is usually associated with abnormality in the clinical response (Kriese, 1923). It would therefore be safest to assay the preparations by both methods and to reject those that do not give concordant results. Those which agree should be adjusted to the U S P standard."

—"A Manual of Pharmacology"—Sollman

Wyeth's Capsules Digitalis Leaf, Defatted, are doubly standardized for the protection of yourself and the patient. They are supplied in vials of thirty-six and one hundred distinctive green capsules.



JOHN WYETH & BROTHER, INC.
PHILADELPHIA PA AND WALKERVILLE, ONT



MORE than thirty years have elapsed since the introduction of PYRAMIDON, and constantly increasing numbers of physicians testify to its dependability and safety as an analgesic in various painful conditions.

Included among these are *headaches, migraine, earache, tabetic pains, tic douloureux, sciatica* and other *neuralgias*, the muscular pains of *colds and influenza, lumbago, acute and chronic rheumatism, dysmenorrhea*.

In these diverse conditions, PYRAMIDON allays suffering without disturbing the *stomach* or *depressing the heart*. Owing to its excellent tolerance, even children are able to take comparatively large doses without untoward effects.

Because of its persistent action, often over many hours, frequent repetition of the dose is generally unnecessary PYRAMIDON also possesses an anti-pyretic property which may be utilized with advantage in acute diseases associated with pain and fever.

DOSE As a general analgesic for adults, one 5 grain tablet or two teaspoonfuls of Elixir of Pyramidon, repeated when pain recurs. For children of 5 years, one 1½ grain tablet or ½ teaspoonful of Elixir.

In acute articular rheumatism, Pyramidon in 5 grain doses, 3 to 6 times daily, has proved effective in many cases.

Sample and literature on request

Pyramidon
BRAND OF AMIDOPYRINE

The
Dependable
Analgesic

Supplied in 5 gr. tablets, tubes of 10 and bottles of 100—1½ gr. tablets, bottles of 25 and 100—Elixir (2½ gr. per teaspoonful) in 4 oz. bottles

H. A. METZ LABORATORIES, INC., NEW YORK, N. Y.



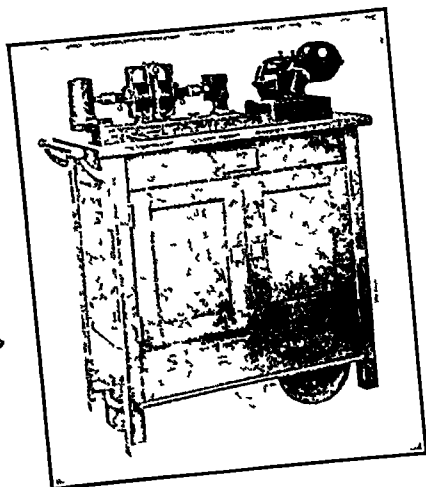
The doctor's time is too valuable to wait for battery service

The new HINDLE "all electric" models operate directly from the house lighting system. The doctor therefore requires no more batteries or battery service, no more embarrassing moments with a dead battery. The new Hindle "All-Electric" Electrocardiograph is ready to take tracings by simply plugging it into the nearest A C outlet. It has always been the acme of accuracy, dependability and durability. This new "All Electric" feature adds convenience.

**CAMBRIDGE
INSTRUMENT CO. INC.**

"Pioneer Manufacturers of the Electrocardiograph"

3732 Grand Central Terminal
New York City



The "all-electric" models are made in stationary, mobile and portable types. All are characterized by their absolute accuracy, dependability, ruggedness, simplicity of operation and compactness of design. They are ideal instruments for use in hospital, clinic or private office.

Send for Literature

HINDLE
"ALL-ELECTRIC"
ELECTROCARDIOGRAPH

Please Mention this Journal when writing to Advertisers

Ipral

SQUIBB

**Recommended for restlessness
and irritability in whatever
conditions these symptoms arise**



Ipral Squibb possesses a wide range of therapeutic uses. It induces sleep closely resembling the normal. In mental and nervous cases associated with insomnia and in combating restlessness and irritability preceding and following major operations it is of particular value.

Ipral (calcium ethylisopropylbarbiturate) is a potent and safe hypnotic—fairly soluble in water and therefore readily absorbed and rapid in effect. Its effect on the

heart, lungs, kidneys or gastrointestinal tract is negligible, even when employed in sufficient amount to produce amnesia.

Ipral is marketed in $\frac{3}{4}$ -gr and 2-gr tablets in vials of 10 and bottles of 100 and 1000. It is also available in powder form in 1-oz. bottles.



*For literature write Professional Service
Department, 745 Fifth Avenue New York*

E·R·SQUIBB & SONS, NEW YORK
MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858.

Vitamins should be prescribed in a group

THE more medical science discovers about the value and functions of vitamins as they affect the health and well-being of the human race, the more vital these mysterious elements become. In an address given before the Medical Association of Georgia, at its Eighty-third annual session held at Savannah, Ga., from May 17 to 20, 1932, Dr. D. H. Garrison, of Tate, Ga., said:

"Study of vitamins from a physiologic and therapeutic standpoint has led to the conclusion that the human system cannot survive without the proper intake of vitamins and that it is as important to have a balanced intake of vitamins as it is to have a balanced intake of food supply. No one vitamin, prescribed alone, can give the proper results, but *vitamins must be prescribed in a group*, or at least the *vitamin A* should be prescribed with any other vitamin in order to obtain the proper results."

This confirms the growing conviction that the prescription of any one particular vitamin in excess is more harmful than beneficial, while, as Dr. Garrison suggests, the intake of a sufficiency of the several vitamins is decidedly beneficial.



Maltine With Cod Liver Oil is widely used because of its known and guaranteed vitamin content. Seventy per cent is Maltine, a concentrated extract of the nourishing elements of malted barley, wheat and oats—rich in Vitamins B and G. The remainder is pure, vitamin-tested cod liver oil, which supplies Vitamins A and D. Taken with orange or tomato juice a fifth vitamin—C, is added. Experience has demonstrated the value of Maltine With Cod Liver Oil in the treatment of metabolisms disturbed by insufficient diet and lack of vitamins.

Maltine With Cod Liver Oil is biologically standardized and guaranteed to contain four vitamins, A, B (b₁), G (b₂) and D. Biological report on request. The Maltine Company, Est. 1875, 30 Vesey Street, New York, N. Y.

Maltine

WITH COD
LIVER OIL



* Journal of the A. M. A. Vol. 98, No. 25, Page 2236

Calcium Deficiencies IN TETANY

"WHEN all the facts of tetany are arrayed it is impossible to escape the impression that there is a fundamental relation between the various types," is the opinion of Peters and Van Slyke.¹

The disorder may take such forms as the spasmophilia of infancy, the tetany of pregnancy, the convulsions of uremia, postoperative tetany, parathyroid tetany, and that associated with osteomalacia.

Cantarow² finds that when serum calcium falls below 7 mg. per 100 c.c. symptoms of tetany are manifest.

Alfred Hess notes that tetany occurs "frequently, in fact generally, in a latent form."³ In view of this the physician must be on guard against tetany in those cases where there is likely to be a drain on the calcium stores, particularly during growth and in pregnancy and lactation. Considering that the average diet is probably lower in calcium than in any other chemical

element, the problem of increasing calcium intake through ordinary foods is difficult. Calcium salts, moreover, are not usually relished by the patient.

A larger intake of calcium alone is not effective, however, unless the body is able to utilize the added minerals. Moreover, tetany is marked by elevations of serum phosphorus, according to Collip.⁴ Thus the problem arises not only of increasing calcium concentration but also of maintaining the proper ratio between calcium and phosphorus. "Vitamin D, as is well known, has remarkable power to regulate calcium and phosphorus metabolism," McCollum observes.⁵

Alfred Hess declares increased calcium intake together with viosterol to be the treatment of choice in tetany.³ He adds the significant comment that in tetany viosterol is characterized by its rapid action, whereas cod liver oil, in infantile tetany at least, appears to act upon the concomitant ricketic condition rather than upon the tetany.

MEAD'S CEREAL

Enriched with mineral and vitamin containing foods

SUPPLIES Calcium

Containing 0.22 Gm. Ca and 0.17 Gm. P per ounce, this delicious cereal is richer in these minerals than most principal foodstuffs. Two ounces supplies as much calcium as 12 ounces of fluid milk and thus obviates the need for excessive quantities of liquid in the diet. It also makes good the iron and vitamin B deficiencies of milk.

MEAD'S VIOSTEROL

IN OIL 250 D

UTILIZES Calcium

Alfred Hess says of viosterol: "One of the distinctive characteristics of this remarkable substance is that it raises the level of either inorganic phosphorus or of calcium, depending on which is in low concentration in the blood or tissues."³ Uniformly potent, accurately assayed, Mead's Viosterol can be depended upon for good results in tetany.

1-5 Bibliography on request.

MEAD JOHNSON & CO., Evansville, Ind., Pioneers in Vitamin Research

See a sample of this remarkable form of VITAMIN D added, ready to serve by simply stirring (with a fork) with water as in a hot drink. The cereal prepared in the cereal bowl in a few moments.

Please Mention this Journal when writing to Advertisers

ANNALS OF INTERNAL MEDICINE

VOLUME 7

JULY, 1933

NUMBER 1

PRESENTATION OF THE JOHN PHILLIPS MEMORIAL PRIZE TO DR. WILLIAM CASTLE

By F M POTTENGER, M D , F A C P , *President, American College of Physicians*

MEDICINE is an unfolding science Great advances have been made by few , but the real test of our profession is its ability to follow its leaders

Doctor Castle, it has been your good fortune not only to be a follower in the first ranks, but to push forward into the unknown Your work on the anemias has added organized knowledge where but a short while ago ignorance blocked our way Your work has rendered so great a service to Medicine that the Committee on the John Phillips Memorial Prize of The American College of Physicians has designated it worthy of unusual recognition

We hope that the insight which you have now attained in this important field will enable you to add still more to our knowledge

Doctor Castle, I take great pleasure in presenting you with the John Phillips Memorial Prize of The American College of Physicians

THE ETIOLOGY OF PERNICIOUS ANEMIA AND RELATED MACROCYTIC ANEMIAS*

By W B CASTLE, F A C P , *Boston, Massachusetts*

DURING the past five years the problem of the etiology of pernicious anemia and other macrocytic anemias responding to liver extract has been investigated at the Thorndike Memorial Laboratory, Boston City Hospital. At various times Dr Wilmot C Townsend, Dr Clark W Heath, Dr Maurice B Strauss and myself have been engaged in this study. Last year, in collaboration with Dr C P Rhoads of the Rockefeller Hospital, the macrocytic anemia of sprue in Puerto Rico was studied under the auspices of the Rockefeller Foundation. Recently Dr Strauss has investigated the mechanism of the pernicious anemia of pregnancy.

The technic first employed was the incubation of various preparations of normal human gastric juice with beef muscle and the administration of the suitably prepared incubated material to cases of pernicious anemia. The presence or absence of hematopoietic effects has been determined by the appearance or non-appearance respectively of significant reticulocyte increases during successive ten-day periods of daily administration of the incubation mixtures. Sufficient experiments of this type have previously been reported to demonstrate that Addisonian pernicious anemia is a deficiency disease conditioned by the lack of a specific intrinsic factor, present in normal human gastric juice and absent in that of cases of pernicious anemia in relapse^{1, 2, 3, 4}. In the normal individual the function of this intrinsic factor of the gastric juice is to interact with an extrinsic factor in the food to produce specific hematopoietic effects (demonstrable in pernicious anemia). Alone, neither normal human gastric juice nor beef muscle has yielded significant hematopoietic responses in pernicious anemia. However, the daily administration of mixtures of beef muscle and gastric juice to suitable patients with pernicious anemia invariably produced reticulocyte increases and when prolonged over several weeks was sufficient to bring the blood and the clinical condition essentially to normal. The interaction of these two factors may, therefore, be regarded as preventive of the development of pernicious anemia in the normal individual. Conversely, the failure of this reaction to take place may be expected to lead to the development of pernicious anemia. Thus, all the patients with Addisonian pernicious anemia in relapse, who have so far been examined, have shown an inability to carry out this essential reaction. It is important to emphasize that these observations demonstrate the existence of a physiological mechanism in the normal individual which

*Address delivered by Dr W B Castle as recipient of the John Phillip Memorial Prize at the Meeting of the American College of Physicians, February 6, 1933.

Presented at the Thorndike Memorial Laboratory, and the Second and Fourth (Harvard) Medical Symposia at Boston City Hospital and the Department of Medicine of the Harvard Medical School.

is absent in the patient with pernicious anemia in relapse. Both the food and the stomach are involved in this process. On the other hand, the demonstration of the hematopoietic activity of various substances such as arsenic, liver, kidney, brain, and even stomach preparations or the injection of milk or gastric juice, does not necessarily establish their etiological relationship to the disease, despite their efficiency in its treatment.

The intrinsic factor of the normal gastric juice has been defined as a heat-labile substance, not corresponding in its properties to hydrochloric acid, pepsin, rennin, or lipase.⁵ Recently Dr. Strauss and I have turned our attention to the extrinsic factor, and incubation of various substances has been carried out with normal human gastric juice. Starting with the results of the previous observations demonstrating that the extrinsic factor of the food has been found in the washed proteins of beef muscle precipitated at pH 6, but not in washed casein or wheat gluten, the former of which is a relatively complete protein,⁴ the work was extended to nucleoproteins and their derivatives. The results of these observations make it clear that nucleoproteins, and nucleic acid from animal sources and from yeast, cannot react effectively with normal human gastric juice. On the other hand, we have now shown that the extrinsic factor is present in autolyzed yeast in approximately 20 times the concentration found in beef muscle. It is not destroyed by autoclaving for five hours at 15 pounds' pressure, which destroys vitamin B₁ but not vitamin B₂, and it is separable from the proteins of yeast by 80 per cent alcohol in which it is soluble.⁶ In addition, the extrinsic factor is found in rice polishings and in wheat germ. Liver extract No. 343 N N R, a source of vitamin B₂, may be rendered inactive in pernicious anemia by hydrolysis with dilute sulfuric acid, a procedure that does not destroy vitamin B₂. If this hydrolyzed material is then incubated with normal human gastric juice, it is again rendered active. In general, then, the characteristics and distribution of the extrinsic factor correspond to those of vitamin B₂.

We⁶ have previously pointed out that there are three possible mechanisms by the action of one or more of which pernicious anemia may be produced, namely, a lack of the specific intrinsic factor of the stomach, a lack of the extrinsic factor of the diet, or a failure of absorption or utilization of the product of the interaction of the intrinsic and extrinsic factors. These postulates can now be extended to include other types of macrocytic anemia and can be shown to be consistent with the supposition that vitamin B₂ is the extrinsic factor.

1 All cases of classical Addisonian pernicious anemia in relapse which we have studied thus far, have been mainly due to the operation of the first mechanism, a lack of the intrinsic factor in the stomach.

2 Sprue with macrocytic anemia, on the other hand, has been successfully treated by Elders⁷ and Ashford⁸ with diets rich in animal protein, and hence rich in vitamin B₂, and more recently we⁹ have had success in certain cases with yeast. Similarly Wills¹⁰ has successfully treated tropical macrocytic anemia with autolyzed yeast alone, and Vaughan and Hunter¹¹

have obtained definite results with the same substance in the macrocytic anemia of celiac disease. These results may now be explained on the basis that in all probability the anemia was mainly due to the second mechanism outlined above, namely, a lack of the extrinsic factor in the diet.

3 It must, however, be remembered that in certain cases of macrocytic anemia, the third possibility, namely, defects of absorption, may be involved. Thus, in certain cases of pernicious anemia and especially in advanced cases of sprue, enormous doses of liver extract given by mouth may be relatively ineffective while the usual parenteral dose gives a typical response⁶. It is possible that various factors within the body may also be involved in these differences. It has also been pointed out that the same mechanism may not always be active. This is best illustrated by certain cases of the pernicious anemia of pregnancy which during pregnancy show no response to beef muscle. After delivery, however, beef muscle produces a reticulocyte response which may be then increased by the addition of normal human gastric juice^{12, 13}. This we interpret as indicating a lack of the intrinsic factor in the gastric juice during pregnancy and its partial recrudescence after parturition. The reappearance of the intrinsic factor has also been observed in one case of pernicious anemia following the improvement induced by liver therapy⁶.

It is now possible to explain why certain cases of macrocytic anemia will respond to both liver extract and autolyzed yeast and others only to liver extract. The difference appears to depend on the presence or absence of the intrinsic factor. In the light of this evidence it is clear that the common factor for producing macrocytic anemia is the failure of the specific reaction between the extrinsic and the intrinsic factors. These anemias should, then, occur both where, on the one hand, the diet is deficient in vitamin B₁₂, and on the other hand, where, although the diet is not grossly deficient, lack of the intrinsic factor is found. Thus, sprue and the macrocytic anemias of the tropics occur in communities or in individuals partaking of defective diets and show gastric anacidity less commonly than is found in patients with Addisonian pernicious anemia, who usually have more normal diet habits. In many cases a combination of gastric defect and dietary deficiency may exist, which would have the same result upon the specific hematopoietic reaction as a total absence of either of its components.

If the evidence be valid that the extrinsic factor of the specific hematopoietic reaction with normal human gastric juice is vitamin B₁₂, a new concept of the relation of certain vitamins to the conditions caused by their lack would seem to be involved. The action of a vitamin in curing a deficiency may thus be essentially dependent upon a specific process in the gastrointestinal tract, and the deficiency state not so much a deficiency in the diet as a deficiency of a reaction in the gastrointestinal tract or elsewhere in the body.

BIBLIOGRAPHY

- 1 CASTLE, W B, and LOCKE, E A Observations on the etiological relationship of achylia gastrica to pernicious anemia, *Jr Clin Investigation*, 1928, *vi*, 2
- 2 CASTLE, W B Observations on the etiologic relationship of achylia gastrica to pernicious anemia I The effect of the administration to patients with pernicious anemia of the contents of the normal human stomach recovered after the ingestion of beef muscle, *Am Jr Med Sci*, 1929, *clxxviii*, 748-764
- 3 CASTLE, W B, and TOWNSEND, W C Observations on the etiologic relationship of achylia gastrica to pernicious anemia II The effect of the administration to patients with pernicious anemia of beef muscle after incubation with normal human gastric juice, *Am Jr Med Sci*, 1929, *clxxviii*, 764-777
- 4 CASTLE, W B, TOWNSEND, W C, and HEATH, C W Observations on the etiologic relationship of achylia gastrica to pernicious anemia III The nature of the reaction between normal human gastric juice and beef muscle leading to clinical improvement and increased blood formation similar to the effect of liver feeding, *Am Jr Med Sci*, 1930, *clxxx*, 305-335
- 5 CASTLE, W B, HEATH, C W, and STRAUSS, M B Observations on the etiologic relationship of achylia gastrica to pernicious anemia IV A biologic assay of the gastric secretion of patients with pernicious anemia having free hydrochloric acid and that of patients without anemia or with hypochromic anemia having no free hydrochloric acid, and of the rôle of intestinal impermeability to hematopoietic substances in pernicious anemia, *Am Jr Med Sci*, 1931, *clxxxii*, 741-764
- 6 STRAUSS, M B, and CASTLE, W B The nature of the extrinsic factor of the deficiency state in pernicious anemia and in related macrocytic anemias Activation of yeast derivatives with normal human gastric juice, *New Eng Jr Med*, 1932, *ccvii*, 55-59
- 7 ELDERS, C Tropical sprue and pernicious anemia, etiology and treatment, *Lancet*, 1925, *i*, 75-77
- 8 ASHFORD, B K Sprue, *Ann Clin Med*, 1925, *iv*, 13-20
- 9 CASTLE, W B, and RHOADS, C P The etiology and treatment of sprue in Porto Rico, *Lancet*, 1932, *i*, 1198-1199, *Trans Assoc Am Phys*, 1932, *xliii*, 245
- 10 WILLS, L Treatment of "pernicious anemia of pregnancy" and "tropical anemia" with special reference to yeast extract as a curative agent, *British Med Jr*, 1931, *i*, 1059-1064
- 11 VAUGHAN, J M, and HUNTER, D The treatment by marmite of megalocytic hyperchromic anemia occurring in idiopathic steatorrhea (celiac disease), *Lancet*, 1932, *i*, 829-834
- 12 STRAUSS, M B Observations on the etiology and treatment of anemia in pregnancy, *Jr Clin Investigation*, 1932, *xi*, 809-810
- 13 STRAUSS, M B, and CASTLE, W B Studies of anemia in pregnancy III The etiologic relationship of gastric secretory defects and dietary deficiency to the hypochromic and macrocytic (pernicious) anemias of pregnancy and the treatment of these conditions, *Am Jr Med Sci*, 1933, *clxxxv*, 539-551

Other cases of widely different type, but in which fatigue was the outstanding complaint, showed definite improvement in the nervous symptoms under treatment with cortin. Mental irritability was decreased, sleep improved and resistance to fatigue, both mental and muscular, was increased. This was not due to suggestion because injections of saline or adrenalin were without effect. Moreover the effect was diminished or absent if the quantity of cortin was too greatly reduced.

In some cases in which definite organic neurological change was accompanied by muscular weakness, cortin caused not only improvement in the motor functions but also a rather striking change in the mental status. Fatigue was diminished with a concomitant increase in strength. Myotonic manifestations and fibrillation, when present, decreased. Depression was replaced by cheerfulness, and a sense of well-being even to the point of euphoria. Irritability disappeared, sleep improved, and erotism became normal in some of the males. These improvements occurred without real changes in the organic neurological state.

Improved motility (in muscular atrophy) may have been brought about by improved strength, diminished fatigue, and increased sense of well-being.

Italian workers⁴ have found that cortical extract is beneficial in certain types of neurasthenia and psychasthenia.

Cortin affects the nervous system in normal individuals under certain conditions. If the subject is in excellent condition effects are not easily detected, but if he is below par, e. g. tired or nervous from overwork or recovering from an infection, response to cortin is quite noticeable. In the course of half an hour he becomes drowsy. While the effect lasts he sleeps more soundly and his sleep is more beneficial so that less sleep than usual may suffice. There may be an increased sense of well-being sometimes to the point of euphoria. Later he may become more alert and seem physically more fit. In a nervous or tired subject an increased reserve seems to be acquired. Certain subjects have shown these responses many times.

We have dwelt at length on the evidence of involvement of the nervous system including the higher centers in the action of cortin because this has been somewhat ignored heretofore.

Muscular Asthenia It is impossible to separate the muscular element from the nervous element except in a muscle preparation. Therefore, any consideration of asthenia in the intact organism involves both the nervous and muscular systems. We have already described experiments which prove that muscle itself is involved in the asthenia.

We have studied the effect of cortin on the resistance of the intact muscles to fatigue. This was measured objectively by means of an ergometer. Positive effects were obtained in widely varying clinical cases and, to a lesser degree, in some normal individuals. Increase in power to work without fatigue was associated with general improvement, although in some instances rising of the fatigue threshold preceded definite subjective sensation of improvement. In a few clinical cases the working power was increased many fold while in normals the increase was only 50 to 100 per cent.

Baird and Albright⁶ found no change in resistance to fatigue, as shown by the ergometer, in their cases of Addison's disease under treatment with cortin except that which might be accounted for by practice. Two out of our six cases tested by the ergometer showed no change under treatment.⁵ In the others, the increased power to work without fatigue often came several weeks after treatment had been started. The practice factor was ruled out.

Eagle, Britton and Kline⁷ found that cortin increased the energy output of normal dogs working on a treadmill up to 100 per cent. However, they do not mention the temperature at which their dogs worked. In the Fatigue Laboratory at Harvard, it has been found that dogs will travel much farther than the best performance obtained by Eagle, Britton and Kline if the surrounding temperature is cool (private communication of Dr. D. B. Dill).

There are many factors undoubtedly involved in muscular asthenia: the nervous factor already mentioned, a circulatory one in some instances, and local changes involving the metabolic activity of the muscle itself. In adrenal insufficiency lactacidogen⁸ and phosphagen⁹ are reduced. Buell, Strauss and Andrus¹⁰ found that the ability of the gastrocnemius muscle, from adrenalectomized animals, to produce lactic acid autolytically was impaired. Likewise, it has been found that lactic acid formation under different conditions of rest and activity in the muscle of adrenalectomized rats is greatly reduced.¹¹

Circulatory Asthenia The blood pressure is usually lower than normal in an advanced case of Addison's disease. The fundamental cause has not been ascertained. Heart action may be feeble. This may be similar in origin to the weakness found in skeletal muscle. However, there is some evidence that the blood vessels themselves may be at fault. The fall in blood pressure which often occurs when the patient changes from a horizontal to a vertical position may be significant. Lack of vasomotor compensation seems to be involved, which in turn includes reflex mechanisms.

Concentration of the blood together with an increase in the relative volume of erythrocytes, according to Rogoff and Stewart¹² (see also Estrada¹³), can be detected in most cases somewhat in advance of the onset of symptoms. Roughly, this change is coincident with that in the non-protein-nitrogen.

Swingle et al.¹⁴ recently found a decline in arterial pressure of 20 to 25 millimeters of mercury in early stages of diminution of blood volume in the dog.

Viale and Bruno¹⁵ in 1927 observed that the viscosity of the blood rose, accompanied by a marked increase in all blood cells, producing mechanical obstruction to the circulation. They suggested that the function of the adrenal was to regulate the proportion of plasma and that loss of plasma was due to increased vascular permeability. Edema of the intestinal mucosa, congestion of the pancreas and spleen, and an increase of water in the muscles were also noted. They attribute the increase of permeability to the nervous system and to changes in vasomotor substances in the blood.

According to Rowntree and Snell¹⁶ (p 198) a decrease in blood volume occurs only in the terminal stage or in crises of Addison's disease. The lowest volumes were found in shock while improvement was followed by recovery in blood volume.

Compensation for hemorrhage fails in adrenal insufficiency.¹⁷ In animals (rats) which do not develop adrenal insufficiency as easily as cats or dogs, the blood volume may show little or no change. Yet the water content in many of the tissues of the body is modified.

In rats we have found that complete removal of the adrenals causes an increase in the water content of many of the tissues, and this occurs in animals not showing a severe degree of insufficiency (figure 1). The increase is

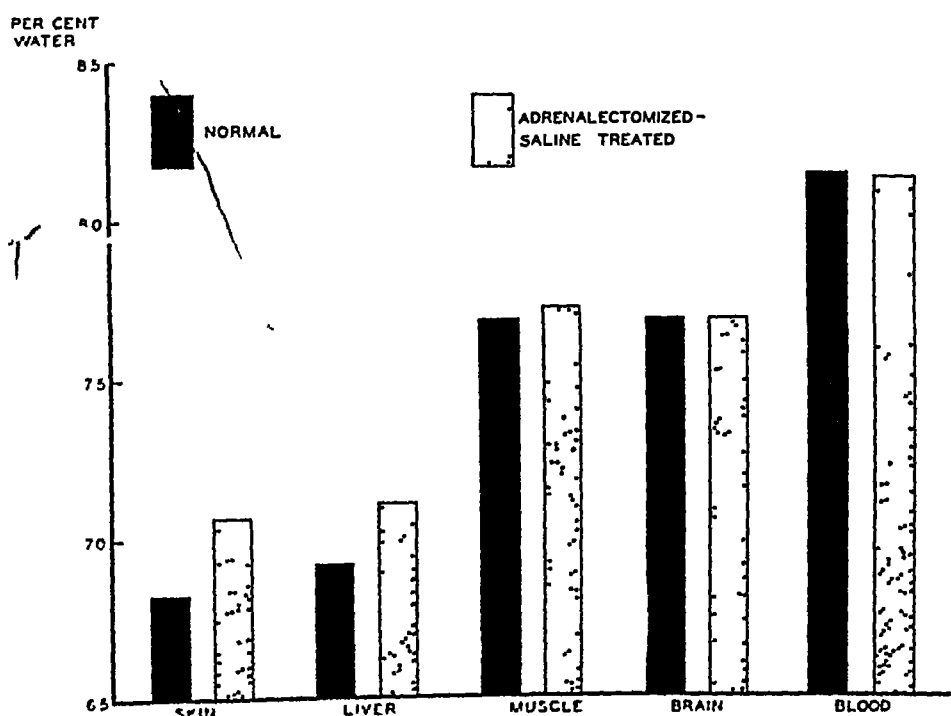


FIG. 1. Water content of tissues in normal (9) and adrenalectomized rats (9) at room temperature (27° C).

largest in skin and liver, is smaller in muscle and very slight in brain. Blood contains the same water content in both normal and adrenalectomized animals. Exposure of adrenalectomized animals to cold or to heat produces less shifting of the water of the tissues in adrenalectomized untreated animals than it does in normal animals. The injection of cortin increases the ability of the tissues to shift water under such stresses.¹⁸ This would account at least in part for the lowered resistance to heat which adrenalectomized untreated animals possess (figure 2), since much of the heat loss is from evaporation of water (in the rat, from expired air and saliva). The slower shift of water may be due in part to inadequate circulation under stress as well to modified permeability.

Durant¹⁹ found that adrenalectomized rats had an average systolic blood

pressure of 77 millimeters of mercury as compared with 112 millimeters for normal rats. This lower pressure developed several hours after the removal of the glands.

How early definite hypotension occurs in Addison's disease is difficult to determine. So often the blood pressure change is not considered significant until the disease is advanced.

In the shock or coma of Addison's disease it is sometimes impossible to correct the anhydremia by administration of fluid subcutaneously or intravenously. On the other hand, a few hours after administration of adequate cortin the readjustment occurs and anhydremia begins to disappear.²⁰ At the same time the blood pressure rises. Swingle et al.¹⁴ emphasize the inability of cortin-insufficient dogs to take up water from the tissues. They believe the fall in blood pressure to be caused by decrease in plasma volume.

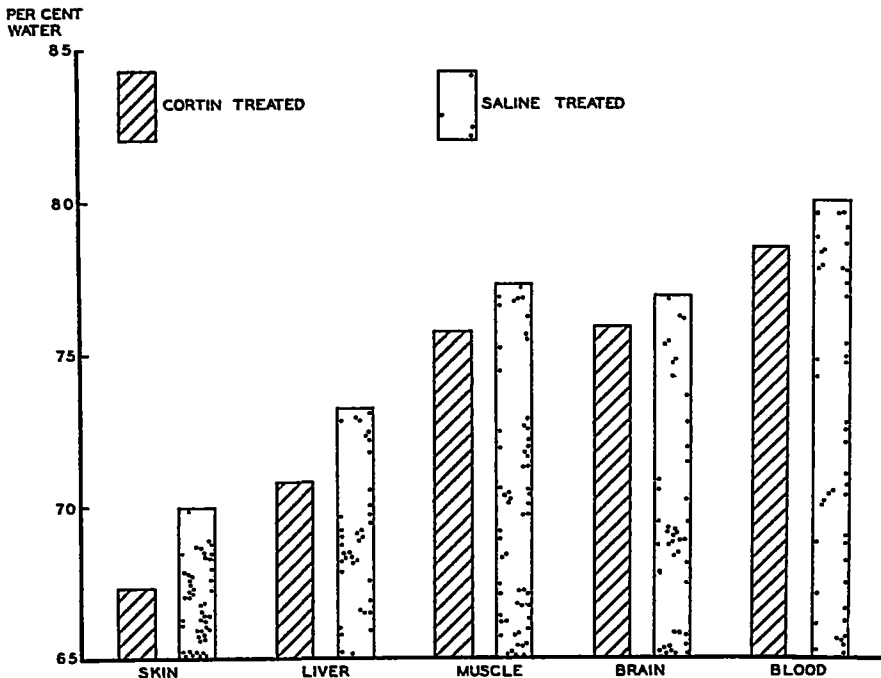


FIG 2 Water content of tissues in adrenalectomized rats after exposure to 37° C, one group (7) injected twice daily with 0.5 cc of cortin and the other (8) twice daily with 0.5 cc of isotonic NaCl solution. The exposure of the NaCl group was for 132 minutes only because of collapse while that of the cortin group was for 191 minutes.

Because cortin does not raise the blood pressure of normal dogs they conclude that it "per se has no effect on blood pressures." This does not follow.

Cortin seems to make the enfeebled heart of an Addisonian patient beat more strongly. It raises the resistance of reflexes to fatigue and thus possibly has an effect on vasomotor tone which in turn influences permeability.

Baird and Albright⁶ found that the poor vasomotor response in Addison's disease was improved by cortin. Cortin may also influence the permeability of tissues as our observations have indicated in the water shift in rats.

The influence of cortin on hypotension in cases of Addison's disease is

not in keeping with other improvements, except when the pressure approaches shock levels. Then cortin, if effective, raises the pressure to 75 or 85 millimeters of mercury within two or three days after which there may be a gradual rise to 90 millimeters or more. However, the pressure commonly remains lower than normal, especially in cases of long standing. We have had cases in which the systolic blood pressure rarely rose above 90 millimeters even with long-continued treatment, yet symptoms of asthenia in the nervous and muscular systems had disappeared. Whether this was due to inadequate dosage or to an irreversible change in the circulatory system remains unsettled. The amount of cortin administered was much less in proportion to that given adrenalectomized animals.

Simpson²¹ likewise finds that the rise in blood pressure upon treatment with cortin is belated and that the upper limits of blood pressure are subnormal.

RENAL INSUFFICIENCY

Following the discussion of circulatory asthenia, we take up that of renal insufficiency because of the possible relationship.

We know that cortin is necessary for normal kidney function because if the subject (whether an adrenalectomized animal or a case of Addison's disease) lives long enough this organ begins to fail. Started in time cortin corrects the condition. In some instances the failure may be attributed to faulty circulation. In others further cause must be sought since the blood pressure does not go low enough to account for the disturbance. Moreover the decrease and recovery of kidney function do not run parallel to the blood pressure changes, there being considerable lag.

That the kidney is directly involved in cortin insufficiency seems to have been shown by the work of Hartman, MacArthur, Gunn, Hartman and MacDonald²² in which it was found that in chronic adrenal insufficiency of cats there was an accumulation of large quantities of lipoid substances in the tubuli contorti.

A more careful study of the kidney in this condition showed degeneration of the convoluted tubules.²³

Harrop, Widenhorn and Weinstein²⁴ believe that the diminished nitrogen and urea output, the lessened volume of urine, and the albuminuria produced by adrenal insufficiency indicate a special influence of the adrenal cortex on kidney function.

It seems impossible in view of the facts to account for the influence of cortin on the kidney entirely through circulatory changes.

GASTROINTESTINAL INSTABILITY

Some Addisonian patients give a history of very early gastrointestinal symptoms while others experience these symptoms much later. These might be accounted for in part by changes in the nervous system. In the later stages, however, circulatory change is a factor. Not only the more sluggish

circulation associated with hypotension but hemorrhages and ulcers which develop indicate a circulatory basis. Cortin stops nausea and vomiting, appetite reappears and weight is regained. In patients the limited amount of cortin injected probably accounts for the failure to reach the former weight level. Doubly adrenalectomized animals not only regain the former weight but with adequate cortin may go beyond. Indeed, this is a test of the potency of an extract (especially in immature animals). Cortin likewise stops the hemorrhage which sometimes occurs from the alimentary canal in late adenal insufficiency in animals.

METABOLISM

It is well known that cortin is necessary for normal metabolism. Aub, Forman and Bright²⁵ in 1922 showed that metabolism was reduced after removal of the adrenals. This is due in part to changes in the metabolism of muscle itself since oxidation is nearly always lower in the muscle of adrenalectomized animals²⁶. In 1928 we²⁷ showed that metabolism of adrenalectomized cats could be maintained within normal limits with very small amounts of cortin. Webster, Pffner and Swingle²⁸ in 1931 confirmed our results and showed further that metabolism could be brought back to normal after allowing animals to pass into the late stages of adrenal insufficiency. They were unable to show an increase in metabolism in normal animals after the injection of cortin. These effects on metabolism were independent of the thyroid.

It has recently been demonstrated (Griffith, Winter and Parsons, unpublished) that cortin has no effect on the basal metabolism in normal human beings.

A limitation of ability to increase metabolism to meet the demands of cold has been shown in cortin insufficiency in animals²⁹. At first untreated adrenalectomized animals maintain a compensatory heat production when exposed to low temperatures. After a short time, however, this fails, and heat production may even fall below what is normal at room temperature. Adrenalectomized animals treated with cortin are able to compensate by producing the extra heat much as do normal animals (figure 3). This failure to produce heat in adrenal insufficiency on exposure to cold is not due to reduction in the blood sugar because it frequently occurs with normal sugar values. Much of the heat production comes from muscular activity. This is reflexly increased upon exposure to cold. The easy fatigue of the reflexes after adrenalectomy may account, in part, for the failure to produce the extra heat. In addition, changes in the heat producing tissues themselves may be partially responsible.

GROWTH

Cortin is essential for growth, whether it be the natural development of the young animal or the renewal of tissue in the healing of wounds. In adrenal insufficiency growth or the healing of wounds may even stop. Upon



FIG 3 Adrenalectomized rats before and after 85 minutes' exposure to 4° C, one group injected twice daily with 0.5 cc of cortin and the other twice daily with 0.5 cc of isotonic NaCl solution. One NaCl treated rat died.

the administration of adequate amounts of cortin growth is resumed at its former rate. This is also true of the healing of tissues. However, the more extensive the injury the greater the amount of cortin required.

RESISTANCE TO TOXINS

It is well known that in adrenal insufficiency there is a lowered resistance to toxins. It has been shown that cortin increases the resistance of adrenalectomized animals to bacterial toxins^{20, 21}. Likewise it has been shown that infections increase the demand for cortin. Adrenalectomized animals which become infected must be injected with considerable amounts of extract in order to recover. Likewise in Addison's disease cases maintained at a constant level with a certain dosage require much more cortin when infections are contracted. Death from a minor infection is not uncommon.

The pathological changes produced in the adrenals from superficial burns²² indicate the possibility of adrenal insufficiency. In such conditions the symptoms which develop are similar to those in adrenal failure. An illustrative case has come under our observation. A child, five years of age, was severely burned on about 30 per cent of her body surface. On the first day she was nauseated. On the second day she became irrational and delirious at times, and there was considerable muscular twitching and irritability. She could not retain liquids. On the third day, her temperature was subnormal and she was seized with a convulsion after which she was sent to the hospital. Fluids were injected together with large amounts of cortin and within twenty-four hours she had come out of the semi-comatose condition and showed general improvement. Within forty-eight hours after institution of treatment with cortin and fluids she could retain fluids by mouth and the children were improving for the first time since the injury. The

response to fluids and cortin was so similar to that obtained in the coma of Addison's disease that we mention it here. The relative parts played by fluid and cortin in the recovery were undetermined.

RELATION OF CORTIN TO VITAMIN C

Cortin seems to have some function in the utilization of certain vitamins.

The changes that take place in the adrenal gland with the development of scurvy indicate possibly an overtax on this gland. The adrenal is rich in vitamin C (hexuronic acid), which (in the guinea pig) is not synthesized to any extent in the body. Therefore its concentration in the adrenal cortex may be significant. We³³ have obtained evidence that cortin aids in the utilization of vitamin C (figure 4). Guinea pigs fed a diet free from this

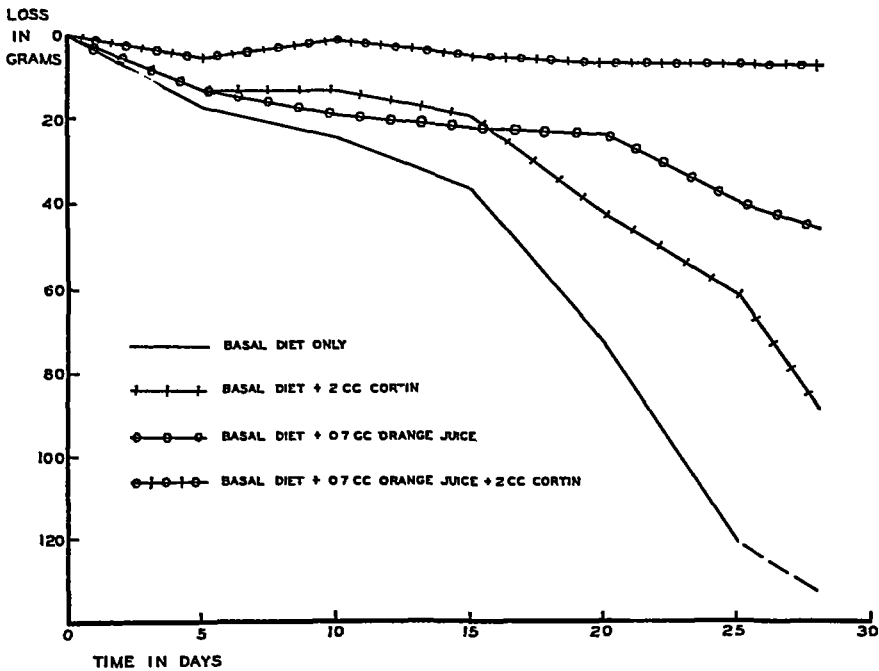


FIG 4 Loss in weight of guinea pigs on a diet in which vitamin C is absent (basal) or inadequate (0.7 cc orange juice) showing influence of daily injections of cortin

vitamin, if injected with cortin, resist scurvy longer than do similar animals without cortin. This is not due to the presence of vitamin C in the cortin extract for in the preparation extraction by ether eliminates it. If guinea pigs are fed a diet containing added vitamin C in amounts inadequate for maintenance they resist scurvy longer if injected with cortin than do animals similarly treated but with cortin omitted. Their response to cortin indicates a better utilization of the available vitamin C.

RELATION TO THE GONADS

There is a good deal of clinical evidence of an intimate connection between sex characters and the adrenal cortex. Tumors of the adrenal body

are sometimes associated with precocious development of the reproductive organs. Hyperplasia of the adrenal gland may be associated with pseudo-hermaphroditism especially in the female. In the latter case the male primary and secondary sexual characters tend to increase at the expense of the female.³⁴

In Addison's disease menstruation may cease and libido in both sexes may diminish or disappear. These may not be direct effects of cortin insufficiency since they could be explained by the lowered activity of the organism generally. Cortical extract may cause the return of menstruation and frequently libido is increased.

Various adrenal preparations have been found to influence the development of the gonads.^{35, 36}

Atwell³⁷ has found that the ovaries of hypophysectomized tadpoles become larger in animals treated with extract containing cortin than in untreated controls. This observation indicates that the action is not through the pituitary.

It has been shown that the interval between menstrual periods can be shortened three to five days in normal women by the injection of cortical extract.³⁸

Pregnancy increases the demand for cortin except in the dog. Elliott and Tuckett³⁹ found that a cat near full term died more speedily after complete adrenalectomy than similarly operated cats not pregnant. In rats we find that pregnancy requires more cortin.

A condition in the human suggesting adrenal insufficiency sometimes develops in pregnancy. In one case of this kind, treatment with cortin resulted in striking improvement.⁴⁰

Whether or not cortin alone is responsible for these influences on the sex organs or whether cortin is merely necessary for the well-being of the rest of the organism, thus indirectly influencing the gonads, while a second hormone affects the gonads directly, remain to be settled.

PIGMENTATION

Although pigmentation is considered one of the cardinal signs in Addison's disease, it is not always present.⁴¹ Even where pigmentation is present it is sometimes impossible to attribute it to Addison's disease because of the similarity to the pigmentation found in other conditions. In four of our cases definite decrease in pigmentation has been shown after the use of cortin.

It is interesting to note that after recovery from a relapse in a severe case of Addison's disease, desquamation over the body may become very marked. In adrenalectomized animals, on the other hand, no proved changes in pigmentation have ever been recorded. There is a change in the skin itself, however. A freshly shaven area in a white cat becomes dirty gray and appears poorly nourished. In the late stages of insufficiency the hair falls out easily or can be pulled out in masses. Administration of cortin to these animals restores the skin to its healthy appearance and the hair again becomes luxuriant.

CHEMICAL CHANGES IN THE ORGANISM

It has been thought that a change in some one substance in the body might account for cortin insufficiency. Many chemical changes have been suggested as responsible. We shall briefly discuss two.

Carbohydrate Metabolism Although it has been known for a long time that the blood sugar was frequently low, especially in the later stages of adrenal insufficiency, no great significance was attributed to this by any one until Britton,⁴² on the basis of certain experiments, concluded that the change in carbohydrate metabolism in adrenal insufficiency was of outstanding importance. Undoubtedly, it is important in many instances, yet the irregularity of its appearance, even in severe cases of insufficiency, would seem to rule it out as the chief effect of adrenal insufficiency.¹⁸

Sodium and Potassium The loss of sodium and the increase in potassium in some instances of adrenal insufficiency likewise suggested a fundamental cause. Baumann and Kurland⁴³ observed a fall in sodium and a rise in potassium of the plasma after adrenalectomy in cats and rabbits. Loeb⁴⁴ has found similar changes in patients with Addison's disease. Marine and Baumann⁴⁵ were able to show that the administration of isotonic solutions of sodium compounds increased the duration of life in adrenalectomized animals. This has been confirmed by a number of workers. The injection of large amounts of isotonic solutions of sodium compounds probably helps to restore the water exchange in tissues. Such injections in adrenalectomized rats increase the ability to form anti-bodies.⁴⁶ Anti-body formation is subnormal in these animals after adrenalectomy.

None of the changes suggested seem to be specific either as a test for adrenal insufficiency or as a primary cause of the condition.

CLINICAL USE OF CORTIN

In order to understand better the clinical use of cortin, let us recapitulate the changes which occur in cortin insufficiency: first and foremost, the asthenias of the nervous system, muscular system and circulation, no one of which is very clearly set apart from the others, renal insufficiency, which may be due in part at least to changes in the kidney itself, gastrointestinal instability, which may have both peripheral and central elements, reduced metabolism and growth, which depend upon the activity of the tissues concerned as well as the general body condition, lowered resistance to toxins, which may be merely another aspect of lowered function in a number of tissues, the increased pigmentation and changes in the skin, and the reduced activity of the sex organs. We speak of these as cortin insufficiencies because this substance is able to correct or abolish them. The relationship to vitamin C deficiency likewise must not be forgotten. At the present time the most reasonable hypothesis seems to be that cortin is a general tissue hormone, but, if for no other reason than the importance of the tissue involved, cortin seems to play a paramount rôle in the function of the nervous system.

With an understanding of the changes that take place in the various

stages of adrenal insufficiency and their responses to treatment with cortin, one has a basis for its clinical use in Addison's disease or any other cortin deficiency

In the early stages of Addison's disease, or in cortin insufficiency in other clinical conditions, there is no criterion for diagnosis. A therapeutic test with cortin seems to be the only means at our disposal to detect the insufficiency. However, a positive response does not necessarily indicate cortin insufficiency since cortin has a pharmacological action in normal subjects.

Conditions for Its Use Asthenias which are unaccounted for by any known cause can be treated with cortin without harm. So far, no one has been able to show deleterious effects in any organism from the use of cortin. It is only when extracts are crude or toxic that care must be taken. One must bear in mind that the responses from cortin are not necessarily immediate. Although they may occur within a few hours, greater effects may appear after two or three days' treatment and sometimes the most marked effects come several days after treatment is discontinued.

It is best to inject once or twice daily for a week or two and then discontinue treatment. This seems to be more effective than occasional treatment every few days. Moreover, it gives a better test of the possibilities of response in the individual.

We have used cortin in a great variety of conditions—and in considerably more than sixty cases. Many others also have employed cortical extracts which undoubtedly contain cortin, the vital hormone of the adrenal cortex.

Although the benefit which is sometimes derived from the use of cortin may at first suggest that the course of the disease has been checked, such improvement may have to be attributed merely to the pharmacological effects of the extract, namely, improvement of the nervous system, better sleep and an increased sense of well-being even to the point of euphoria. Usually such effects are only temporary. Therefore, too much must not be expected when a positive response is obtained.

Dosage can be determined only by trial, but three to ten cubic centimeters per day of a potent extract (the product of 30 gm. of cortex to each cubic centimeter) should give a positive result in any but severe cases, especially if the treatment be continued for four or five days.

Treatment of Addison's Disease In known cases of cortin insufficiency, such as Addison's disease, due regard should be given to the conditions which increase the demand for cortin in order to avoid them.^{35,47} These are infections, toxins, exposure to heat and cold, dehydration, strenuous exercise, worry, indeed any stress which taxes the organism. In normal animals evidence of increased activity in the adrenals under stress is found in their enlargement (table 1).

Treatment with cortin may be intermittent in mild cases of Addison's disease, the dosage being determined by trial. The amount injected daily should at first be gradually increased until a response is obtained. It is well

TABLE I
Influence of Various Stresses on Adrenal Weight

Stress	No of rats	Adrenal weight Per cent gain over controls	Cortex Per cent gain	Medulla Per cent gain
I Exercise	12	14.29	9.2	19.0
II Cold	42	10.90		
III Trauma	12	5.45		
IV Toxin	12	22.90	38.0	23.8
I 1200 meters in two hours five days a week until 12 exercise periods had been run				
II Exposed to cold 20 to 75 hours in from 3 to 14 days				
III Small piece of tail or skeletal muscle removed twice a week for five weeks				
IV Injected daily with dead <i>Staphylococcus aureus</i> for 30 days increasing from 5 billion, first week to 25 billion, last week				

to maintain treatment for a few days until the patient seems to have reached an optimum when treatment may be discontinued for a period. With each sign of cortin insufficiency it is best to resume treatment immediately because the patient tends to go a little farther down hill with each exacerbation. Subcutaneous injection is preferred because of the slower absorption and the ease of accomplishment. The intravenous route is employed in emergencies.

In more severe cases continuous treatment seems on the whole desirable because one is substituting cortin for adrenals that are entirely inadequate. One must also bear in mind that the stage of irreversibility may be unexpectedly reached.

Irreversibility In the terminal stage of Addison's disease cortin sometimes fails to bring about recovery. This might be due to inadequate dosage or to the development of an irreversible condition. That the latter is sometimes true is indicated by the work of Hartman and Winter⁴⁸. They found sometimes that doubly adrenalectomized animals (cats, guinea pigs and monkeys) that had developed a crisis spontaneously or as a result of exercise, could not be more than temporarily benefited by the administration of large amounts of cortin. This stage of irreversibility seems to vary in different individuals and may develop with few premonitory symptoms. It seems to develop more readily under stress, e.g. toxins and exercise. Repeated relapses to the point of prostration seem to make recovery more difficult. Death may occur suddenly with little warning. Patients suffering from Addison's disease sometimes die under treatment with cortin because exacerbation of symptoms is not accepted as indicating that increased dosage should be speedily instituted. Bearing these points in mind, we find it good practise to inject cortin immediately upon exacerbation of symptoms. The patient is carefully watched and if improvement is not shown within two hours additional injections in increasing amounts are made until improvement occurs. The dosage and frequency may then be gradually decreased as long as the optimum condition of the patient is maintained.

SUMMARY

1 An account of the possible functions of cortin is given to serve as a basis for clinical use of the hormone

2 The foremost symptoms of cortin insufficiency are asthenias of the nervous, muscular and circulatory systems The effects of cortin on these systems indicate a paramount rôle in their functions Because of the commanding place occupied by the nervous system in the organism the function of cortin in its activity is outstanding

3 In addition, cortin seems to play a rôle in the activity of other tissues including the kidney, gastrointestinal system, and the gonads

4 General aspects of the problem are the influence on metabolism, growth, resistance to toxins, and changes in the skin and mucosa

5 A newly discovered function of cortin is the part that it seems to play in the utilization of the antiscorbutic vitamin Guinea pigs fed a diet deficient in the latter, resist scurvy longer if injected with cortin than do similar animals without cortin

6 Thus far, none of the chemical changes suggested seems to be specific either as a test for adrenal insufficiency or as a primary cause of the condition

7 The use of cortin in Addison's disease and other clinical conditions in which asthenia is an outstanding symptom is discussed

8 The danger of the development of an irreversible stage in severe cases of adrenal insufficiency is stressed

BIBLIOGRAPHY

- 1 GANS, H M, and MILEY, H H Studies on vigor IX Ergographic studies on adrenalectomized animals, *Am Jr Physiol*, 1927, lxxxii, 1-6
- 2 HARTMAN, F A, and LOCKWOOD, J E Effect of cortin on the nervous system in adrenal insufficiency, *Proc Soc Exper Biol and Med*, 1931, xxix, 141-142
- 3 HARTMAN, F A, BECK, G M, and THORN, G W Improvement in nervous and mental states under cortin therapy, *Jr Nerv and Ment Dis*, 1933, lxxvii, 1-21
- 4 SALERNI, A Sulle Applicazioni Terapeutiche dell'estratto di Corteccia Surrenale, *Giornale del Medico Practico*, 1929, xi, 381 (See additional references in this paper)
- 5 HARTMAN, F A, and THORN, G W The effect of cortin in asthenia, *Proc Soc Exper Biol and Med*, 1931, xxix, 48-50
- 6 BAIRD, P C, JR, and ALBRIGHT, F Treatment of Addison's disease with cortin (Hartman), report of 4 cases, *Arch Int Med*, 1932, i, 394-409
- 7 EAGLE, E, BRITTON, S W, and KLINE, R The influence of cortico-adrenal extract on energy output, *Am Jr Physiol*, 1932, cii, 707-713
- 8 HOUSSAY, B A, and MAZZOCCO, P Variations du glycogène cardiaque et cérébral, de l'acide lactique et du lactacidogene musculaire chez les Rats décapsulés, *Compt rend. Soc. de Biol*, 1927, xcvi, 1252-1253
- 9 LANG, K Nebennierenrinde und Muskelchemismus, *Arch f d ges Physiol*, 1931, ccxxix, 60-85
- 10 BUELL, M V, STRAUSS, M B, and ANDRUS, E C Metabolic changes involving phosphorus and carbohydrate in the autolyzing gastrocnemius and cardiac muscle of normal, of thyroxinized and of adrenalectomized animals, *Jr Biol Chem*, 1932, xcvi, 645-669
- 11 ARVAY, A V, and LENGUEL, L Die Milchsäurebildung bei Muskelarbeit nach Entfernung der Nebennieren, *Biochem Ztschr*, 1931, ccxxxix, 128-137

- 12 ROGOFF, J M, and STEWART, G N Studies on adrenal insufficiency in dogs II Blood studies in control animals not subjected to treatment, *Am Jr Physiol*, 1926, lxxviii, 711-729
- 13 ESTRADA, O P El volumen sanguineo en la insuficiencia suprarenal, *Rev Soc Argentina Biol*, 1926, ii, 367
- 14 SWINGLE, W W, PFIFFNER, J J, VARS, H M, BOTT, P A, and PARKINS, W M The function of the adrenal cortical hormone and the cause of death from adrenal insufficiency, *Science*, 1933, lxxvii, 58
- 15 VIALE, G, and BRUNO, A A Le sang dans l'insuffisance surrenale, *Compt rend Soc de Biol*, 1927, xcvi, 261-263
- 16 ROWNTREE, L G, and SNELL, A M A clinical study of Addison's disease, 1931, W B Saunders Co, Philadelphia
- 17 SATO, H, WADA, M, and KAIWA, T Variation of the blood pressure and blood sugar content of the suprarenalectomized dog after hemorrhage, *Jap Jr Med Sci*, 1931, ii, 90
- 18 HARTMAN, F A, BROWNELL, K A, and LOCKWOOD, J E Studies indicating the function of cortin, *Endocrinology*, 1932, xvi, 521-528
- 19 DURANT, R R The blood pressure of adrenalectomized rats, *Am Jr Physiol*, 1928, lxxv, 364
- 20 HARTMAN, F A, AARON, A H, and CULP, J E Use of cortin in Addison's disease, *Endocrinology*, 1930, xiv, 438-442
- 21 SIMPSON, S L Addison's disease and its treatment by cortical extract, *Quart Jr Med*, 1932, i, 99
- 22 HARTMAN, F A, MACARTHUR, C G, GUNN, F D, HARTMAN, W E, and MACDONALD, J J Kidney function in adrenal insufficiency, *Am Jr Physiol*, 1927, lxxxii, 244-254
- 23 GUNN, F D Anatomical changes following total adrenalectomy in cats, with special reference to the kidney, *Buffalo Gen Hosp Bull*, 1927, v, 13-16
- 24 HARROP, G A, WIDENHORN, H, and WEINSTEIN, A Metabolism studies with an adrenal cortex hormone, *Munch med Wchnschr*, 1932, lxxix, 171-172
- 25 AUB, J C, FORMAN, J, and BRIGHT, E M The effect of adrenalectomy upon the total metabolism of the cat, *Am Jr Physiol*, 1922, lxi, 326-348
- 26 ESTRADA, O P, and NEUSCHLOSZ, S M Las oxidaciones celulares en algunos tejidos de animales suprarenalectomizados, *Rev Soc Argentina Biol*, 1926, ii, 597
- 27 HARTMAN, F A, GRIFFITH, F R, JR., and HARTMAN, W E Observations upon adrenalectomized cats treated with the cortical hormone, *Am Jr Physiol*, 1928, lxxxvi, 360-370
- 28 WEBSTER, B, PFIFFNER, J J, and SWINGLE, W W Effect of adrenal cortical hormone upon respiratory metabolism of normal, thyroidectomized and thyroidectomized-adrenalectomized cats, *Proc Soc Exper Biol and Med*, 1931, xxviii, 1021-1022
- 29 HARTMAN, F A, BROWNELL, K A, and CROSBY, A A Relation of cortin to maintenance of body temperature, *Am Jr Physiol*, 1931, xcvi, 674-689
- 30 PERLA, D, and GOTTESMAN, J M Injections of cortin on resistance of suprarenalectomized rats, biological assay of extracts of suprarenal cortex, *Proc Soc Exper Biol and Med*, 1931, xxviii, 475-477
- 31 HARTMAN, F A, and SCOTT, W J M Protection of adrenalectomized animals against bacterial intoxication by extract of adrenal cortex, *Jr Exper Med*, 1932, lv, 63-69
- 32 WEISKOTTEN, H G Histopathology of superficial burns, *Jr Am Med Assoc*, 1919, lxxii, 259-261
- 33 LOCKWOOD, J E, HARTMAN, D G, and HARTMAN, F A Relation of the adrenal cortex to the development of scurvy, *Proc Soc Exper Biol and Med*, 1933, xxx, 560-562
- 34 GLYNN, E E The adrenal cortex, its rests and tumors, its relation to the other ductless glands, and especially to sex, *Quart Jr Med*, 1911-12, v, 157-192
- 35 HOSKINS, R G, and HOSKINS, A D The effects of suprarenal feeding, *Arch Int Med*, 1916, xvii, 584-589

- 36 COREY, E L, and BRITTON, S W Induction of precocious sexual maturity by cortico-adrenal extract, *Am Jr Physiol*, 1931, xcix, 33-43
- 37 ATWELL, W J Effects of administration of cortin to the hypophysectomized rat, *Proc Soc Exper Biol and Med*, 1932, xxix, 1259-1260
- 38 HARTMAN, F A, GREENE, C W, BOWEN, B D, and THORN, G W Further experience with cortin therapy, *Jr Am Med Assoc*, 1932, xcix, 1478-1483
- 39 ELLIOTT, T R, and TUCKETT, I Cortex and medulla in the suprarenal glands, *Jr Physiol*, 1906, xxxiv, 332-369
- 40 HARTMAN, F A, THORN, G W, and POTTFER, I W Cortin in a case of possible adrenal insufficiency during pregnancy, *Endocrinology*, 1932, xvi, 155-156
- 41 LEWIN, G Über Morbus Addisonii, *Charité-Ann*, 1892, xvii, 536-739
- 42 BRITTON, S W Evidence on the chief function of the adrenal cortex, *Endocrinology*, 1932, xvi, 633
- 43 BAUMANN, E J, and KURLAND, S Changes in inorganic constituents of blood in suprarenalectomized cats and rabbits, *Jr Biol Chem*, 1927, lxxi, 281-302
- 44 LOEB, R F Chemical changes in blood in Addison's disease, *Science*, 1932, lxxvi, 420-421
- 45 MARINE, D, and BAUMANN, E J Duration of life after suprarenalectomy in cats and attempts to prolong it by injections of solutions containing sodium salts, glucose and glycerol, *Am Jr Physiol*, 1927, lxxxi, 86-100
- 46 GOTTESMAN, J M, and PERLA, D Immunological studies in relation to the suprarenal gland V The effect of repeated injections of solutions containing sodium salts and glucose on hemolysin formation of normal and suprarenalectomized rats, *Jr Exper Med*, 1929, l, 93-102
- 47 HARTMAN, F A, THORN, G W, LOCKIE, L M, GREENE, C W, and BOWEN, B D Treatment of Addison's disease with extract of suprarenal cortex (cortin), *Jr Am Med Assoc*, 1932, xcvi, 788-793
- 48 HARTMAN, F A, and WINTER, C A Irreversibility in adrenal insufficiency, *Endocrinology*, 1933, xvii, 180-186

DIFFERENTIATING SOME FUNCTIONS OF THE ANTERIOR PITUITARY HORMONES^{*}

By OSCAR RIDDLE, PH D , *Cold Spring Harbor, New York*

ABOUT twenty different physiological effects have already been found to follow the ablation of the anterior pituitary, or to appear in response to supplements of this tissue or its extracts when injected into intact animals. Some of those who have described such effects have wisely refrained from the conclusion that a particular effect necessarily represents a direct and specific response to an anterior lobe hormone. During the years ahead of us the number of truly direct and specific effects, as well as of others of quite secondary and non-specific nature, may be expected to multiply.

In much that I may venture to say on this somewhat inaccessible field of study I speak with no air of finality, also, I must beg permission to mention only half of this group of responses, and to discuss only four of them. The great difficulty confronting investigation in this field is that we are not yet sure that all of the anterior lobe hormones have been isolated or recognized, and that none of those now known has been isolated in absolutely pure form. Indeed, as this paper must indicate, practically all of the preparations hitherto used can be shown to be mixtures containing two or more hormones in addition to other foreign substance.

Clinical studies provided early and numerous instances of functions or functional disturbances associated with the anterior pituitary. The ablation of the pituitary of the immature frog and mammal, and also that of man—work with which the names of P. E. Smith, B. M. Allen and of Cushing are so much associated—resulted in much basic information as to the rôle of this organ in development, in maturity, and in disease. Together with the repair effected by later anterior lobe supplements the responses of the young to hypophysectomy made it clear that this organ contributes something essential to body growth and to the *development* of the sex organs (gonads), the thyroid and the adrenal cortex. These are four responses with which sound thinking concerning the functions of the pituitary may well begin.

From a different approach to this question a real advance has been made in the detection of the number and types of hormones produced by this gland. Evans and Long¹ disclosed a growth hormone. Smith² and Zondek and Aschheim³ simultaneously certified the existence of a sex maturity or gonad-stimulating principle. The complete distinctiveness and unrelatedness of those two hormones—growth- and gonad-stimulating—has been sharply questioned by Evans, Meyer and Simpson,⁴ but the experience of our own laboratory leaves us nearly or quite convinced of their complete individuality.

Much has been written recently concerning a "luteinizing" hormone of

^{*} Paper read at a general session of the Seventeenth Meeting of the American College of Physicians, Montreal, February 7, 1933.

From the Station for Experimental Evolution, Carnegie Institution.

anterior pituitary origin I believe that the evidence adduced is wholly inadequate, and that the phenomena of luteinization rest upon an explanation which we shall attempt to give elsewhere

We now turn to a consideration of two specific responses, and of a new and third pituitary hormone That something contained in the anterior pituitary is responsible for activating the developed mammary gland to the secretion of milk was shown by Stricker and Gruter^{5, 6, 7}, this result has been confirmed by Corner⁸ and others Again, Riddle and Braucher⁹ showed that the development and secretion of the crop-gland in pigeons is also a specific response to one or another hormone of the anterior pituitary Quite recently Riddle, Bates and Dykshorn have been able to demonstrate the presence of a hitherto unrecognized hormone of the anterior lobe, and to show that the lactation and crop-gland responses are wholly ascribable to this third pituitary hormone This new hormone we have called "prolactin" Since the two above-mentioned responses are so clearly dependent on this new hormone, and the description of these points is only now in press, or has appeared only in preliminary notices (Riddle, Bates and Dykshorn^{10, 11, 12}), I must here give considerable attention to this aspect of the subject In doing this we shall incidentally find clear proofs that some of the most currently used pituitary extracts are mixtures of two or three distinct hormones

In the tabulations which follow we are obliged to give only condensed and rather smooth parts of the voluminous data of Riddle, Bates and Dykshorn, who have used more than 600 animals for these tests The data of table 1 show that the two types of preparation of "growth" hormone used also contained very considerable amounts of the gonad-stimulating hormone, since the testes of all treated animals show a marked increase in size* That the preparations did, in fact, contain the "growth" principle is indicated by the rapid and consistent increase of body weight in treated animals That some of these preparations did, while others did not, contain prolactin is shown by the weights of the crop-glands We find that an unstimulated single crop-gland of an immature ring dove weighs less than 200 milligrams, and that weights in excess of that amount indicate the presence of prolactin The greater the amount of prolactin used the greater is the increase of weight in the crop-gland The duration of the dosage is another factor in this response, we find the maximum weight increase in this gland is attained at the end of seven days, dosage during either longer or shorter periods probably yields less than the maximum response

Our own preparations of the gonad-stimulating (or sex maturity) hormone cause good testis growth, loss of body weight, and no crop-gland response They are therefore free from prolactin, and apparently contain little or none of the growth hormone Prolonged dosage with this hormone causes disproportionately heavier testes (Riddle¹³) than does a shorter term

* A preliminary test of a preparation of the growth hormone of Collip, Selye and Thomson has indicated that it is quite free of demonstrable amounts of the gonad-stimulating hormone, this gives their preparation a wholly unique position among those now available for our tests

TABLE I

The Hormones Present in Various Anterior Pituitary Extracts, as Determined by Injection into Immature Male Ring Doves (Excerpt from Data of Riddle, Bates and Dykshorn)

Dosage				Age of bird	Body weight		Testes		Weight single crop- gland
Preparation		Per day	Dura- tion		Start	End	Test animal	Average control	
Kind	No								
		cc	days	mos	grams		milligrams		mgms
Growth hormone (of Lee and Schaffer)	36	0.4	5	3.3	142	170	61.7	13.9	140
	00	0.5	4	2.5	155	168	43.1	6.7	218
Growth hormone Phyone (Van Dyke)	—	0.4	8	2.8	150	173	50.5	8.5	245
	—	0.8	7	2.8	161	193	50.7	8.5	230
Gonad-stimulating* (our own preparations)	30	0.5	5	2.7	153	140	43.0	7.6	175
	43	0.5	5	2.7	160	148	70.4	7.6	150
"Luteinizing" (Method Hisaw et al) (our own)		0.5	7	2.9	174	165	86.2	8.7	780
Antuitrin 2966759 (Parke, Davis Co) 095029-B		0.2	4	2.5	157	148	16.2	6.7	185
		0.3	9	2.7	132	132	67.0	7.6	160
Prolactin (our own)	11a†	4‡	4	2.6	145	146	15.3	7.0	290
	23	10	4	2.6	148	154	7.5	7.0	985
	29	10	5	2.1	164	162	3.9	6.0	880
	34	10	5	2.4	137	118	3.0	6.8	840
	41	4	4	2.5	135	140	6.8	6.7	410

* Traces of posterior lobe hormones present

† This preparation (11a) contaminated with traces of gonad-stimulating hormone

‡ Prolactin dosage is expressed in milligrams, usually 0.4 or 0.5 cc of fluid was used

of dosage. The "luteinizing fraction" of Fevold, Hisaw and Leonard¹⁴ is clearly a mixture of gonad-stimulating and prolactin hormones. Commercial antuitrin (Parke, Davis and Co) contains only the gonad-stimulating (and thyroid-stimulating) principle in amounts demonstrable in our animals. Our preparations of prolactin are shown to be free of the gonad-stimulating hormone, they should contain little or no growth hormone, and they cause marked enlargement and functioning ("crop-milk" secretion) of the crop-glands.

In table 2 it can be seen that lactation in guinea pigs and rabbits is produced by only those particular preparations which in table 1 produced the crop-gland response. Growth or gonad-stimulating hormones fail to activate the mammary gland to the secretion of milk. The new hormone, prolactin, accomplishes this specific activation in normal and castrate females, and even in suitably prepared normal and castrate males (Riddle, Bates and Dykshorn^{10, 11, 12}).

Two additional responses, liver and thyroid enlargement, the latter thought to be a specific response to a principle contained in the anterior

TABLE II

Showing that Milk *Secretion* in Guinea Pigs and Rabbits Results from the Injection of Prolactin and Not from the Other Two Anterior Pituitary Hormones (Excerpt from Data of Riddle, Bates and Dykshorn)

Kind and condition of animal	Body weight	Pituitary derivative			Result, including date of beginning lactation
		Type or description	Number	Daily dosage	
	grams			cc	
♂, young (RW)*	393	<i>Guinea pigs</i> Prolactin	23	1 0	Lactation 4th day
♀, parous (13)	748	"	29	2 0	Lactation 3rd day
♀, " (2)	645	"	34	2 0	Lactation 3rd day
♂, castrate (R S)*	490	"	41	2 0	Lactation 5th day
♀, parous (4)	530	Growth (+ matur)	00†	1 0	No lactation (6 days)
♀, parous (5)	558	"	00	1 0	" " (6 days)
♀, parous (11)	810	Maturity‡ (own)	30	3 0	No lactation (8 days)
♀, " (15)	660	"	30	3 0	" " (6 days)
		<i>Rabbits</i>			
♀, mature (10)	3400	Prolactin	29	3 0	Lactation on 3rd day
♀, castrate (AJ)	3100	"	34	2 7	Lactation on 3rd day
♀, castrate (Gr)	3700	"	41	4 0	Lactation at 3½ days
♀, mature (Ep)	3000	Growth (+ matur)§	—	1 4	No lactation (6 days)
♀, mature (22)	3600	"	—	3 0	" " (10 days)
♀, mature (3)	3300	Maturity‡ (own)	30	3-6	No lactation (6 days)
♀, mature (P)	5400	"	43	8 0	" " (4 days)

* Preliminary treatment for mammary growth with theelin and progestin

† The preparation of Lee and Schaffer

‡ Used as a synonym for the "gonad-stimulating" hormone, and contains traces of posterior lobe hormones

§ Phylene, prepared by the Wilson Laboratories, method of Van Dyke and Wallen-Lawrence

pituitary, will next be considered. At least a tentative examination of these responses is possible on the basis of such separation and classification of anterior lobe hormones as is provided by the data of table 1.

Smith and Engle¹⁵ noted that the livers of immature rats given pituitary transplants for periods longer than four days were apparently significantly enlarged. The restoration or repair of the thyroid in hypophysectomized tadpoles had long before been observed after parenteral administration of pituitary by Allen¹⁶ and the Smiths¹⁷. Otherwise, Riddle and Flemion¹⁸ were first to report that aberrant thyroids and livers result from (the glycerin extract and suspension of) pituitary tissue repeatedly administered (intraperitoneally) to full grown animals (doves). Riddle and Polhemus¹⁹ showed that an extract (beef) prepared for a high concentration of the growth principle, and another (sheep) prepared for high concentration of the gonad-stimulating principle (but each doubtless containing the other, in addition to other anterior pituitary derivatives) both markedly and regularly produced enlargement of the livers and thyroids of young doves and pigeons.

of both sexes Apparently no other studies have reported a response in the liver from anterior pituitary administration, but Putnam, Benedict and Teel²⁰ produced in dogs a general body overgrowth with which they report an associated general macrosplanchnia Tables 3 and 4 provide further

TABLE III

Liver and Thyroid Response in Ring Doves Obtained from Hormones (or Preparations) of the Anterior Pituitary (Excerpt from Data of Riddle, Bates and Dykshorn)

Preparation		Daily dosage			Body weight		Age	Liver		Thyroid		Crop-gland active (+) or not (-)
Kind	No	Volume	Mgm	Duration	Start	End		Test	Control (an av)	Test	Control (an av)	
		cc		days	grams		mos	grams		milligrams		
Growth (+ maturity) (Lee and Schaffer)	36	0.2	1.5	5	139	144	3.1	6.32	2.0-4.0	21.9	14.8	-
		0.2	1.5	5	113	113	3.0	4.43		42.0	20.0	-
		0.3	2.2	9	137	146	3.2	6.12		65.9	20.0	-
		0.3	2.2	10	142	170	3.3	10.06		36.5	14.8	-
		0.6	4.5	9	134	153	3.3	7.80		37.5	(14.1)	-
		0.6	4.5	10	128	134	3.3	6.51		67.0	(26.4)	-
Growth (+ maturity) (traces Prolactin) Phyone (Van Dyke)		0.4	(4)	6	172	182	14.0	10.06	2.0-4.0	41.5	15.3	(+)
		0.4	(4)	7	160	174	14.0	12.05		41.7	15.3	-
		0.8	(8)	5	137	138	2.8	4.42		29.3	13.9	(+)
		0.4	(4)	8	152	164	2.8	4.21		22.3	13.9	(+)
		0.4	(4)	8	150	173	2.8	5.81		44.3	15.3	(+)
		0.8	(8)	7	161	193	2.8	6.00		39.8	15.3	(+)
Gonad-stimulating (+ traces Pituitrin) (own preparations)	36a	0.2	?	5	134	127	2.8	2.15	3.03	26.4	20.3	-
		0.2	?	5	144	136	2.8	2.67	3.03	28.4	20.3	-
	56	0.5	2.2	6	157	141	2.9	2.91	3.33	29.2	20.1	-
		0.5	2.2	6	160	144	3.3	2.44	2.95	52.0	(23.0)	(+)
	43	0.5	3.5	5	143	139	2.9	2.63	2.87	43.9	20.0	-
		0.5	3.5	5	143	130	2.9	2.71	2.87	72.9	20.0	-
		0.5	3.5	5	160	148	2.7	2.62	2.60	24.7	15.3	-
		0.5	3.5	7	172	166	13.7	3.05	2.79	60.8	13.9	-
		0.5	3.5	8	165	162	12.3	2.98	2.95	61.8	(23.0)	-
Prolactin (own preparations)	11a*	0.4	4.0	4	145	138	2.8	3.07	3.33	14.8	20.1	++
		0.4	4.0	4	145	146	2.6	3.25	3.35	36.2	26.2	++
		0.5	10.0	4	152	164	13.5	6.85	3.32	25.2	(14.1)	+++
		0.5	10.0	4	145	146	2.7	3.51	3.35	30.0	26.2	+++
		0.5	10.0	4	132	133	2.8	4.05	3.33	12.7	20.1	+++
		0.5	10.0	4	181	162	2.8	3.42	3.07	10.5	(14.1)	++
	69	0.5	10.0	4	116	110	3.0	2.88	2.87	22.9	20.0	++
		0.5	10.0	7	137	134	3.1	3.07	2.87	10.7	20.0	+++
		0.5	10.0	7	152	137	2.9	3.16	3.02	13.5	(11.9)	+++

* Traces of gonad-stimulating hormone in preparation No 11a

data concerning this response of the liver—a response which indeed may be non-specific and of mixed and secondary origin Our earliest indication of a size increase in the thyroid from something contained in the

anterior pituitary extracts has been fully confirmed and developed much further by others. Loeb and Bassett,²¹ Aron²² and others got thyroid hypertrophy in mammals, with definite evidence for increased thyroid function. Schockaert²³ supplied similar evidence from the duck.

The next step to be taken—and the one undertaken in the following paragraphs—is to identify the particular anterior pituitary hormone responsible for liver enlargement and for thyroid enlargement. On this point it should be noted that an early and remarkable study of Smith and Smith²⁴ clearly indicated that the pituitary principle that reacts with the endocrine system is separate (even topographically) from that controlling body growth. This view was supported by Evans²⁵. Later, Smith²⁶ supplied cogent evidence for the view that *two* anterior pituitary hormones affect thyroid structure and activity, one—apparently the gonad-stimulating—stimulates the thyroid, while the other—the growth hormone or another one associated with it in the earlier prepared alkaline extracts—depresses the thyroid. Crew and Wiesner,²⁷ from observations on batrachians, found it probable that there is a separate and distinct thyreotropic hormone. Aron²⁸ inclines, though with some reserve, to the view that it is the gonad-stimulating hormone that induces the response in the thyroid. Loeb²⁹ from extensive studies on guinea pigs, concludes there is no connection between gonad growth and thyroid hypertrophy, but a tendency of certain anterior pituitary preparations simultaneously to inhibit full follicular growth, produce lutein bodies, interstitial glands and hypertrophy of the thyroid. The uncertainty and contradictions expressed above are traceable, I believe, to two sources, namely, to the mixed and largely unknown hormone content of the extracts necessarily used hitherto, and to the unsuitability of the rodent ovary for the assay of the gonad-stimulating hormone in unpurified *extracts* (not implants) of the pituitary.

The data of table 3 show that the growth hormone of Lee and Schaffer and that of Van Dyke and Wallen-Lawrence (phyone) gave good increases in body weight in our tests. Our complete assays of these preparations show that they contain the gonad-stimulating hormone in addition to that for growth. One preparation of Lee and Schaffer was free of prolactin, while phyone contains traces of prolactin. The tabulated data show that both preparations cause prompt enlargement of both the liver and the thyroid, to this there is no exception. All of the liver responses shown here were caused by extracts rich in *two* potent hormones which probably never coexist in such quantity in a normal animal. The response may therefore be definitely pathological, not physiological.

Let us next note the effects of some quite good preparations of the gonad-stimulating hormone prepared in collaboration with Dr. Bates in our own laboratory. The injection of these preparations causes our animals to lose weight and, in the quantities used by us, they show no prolactin. They are indeed known to be contaminated with the posterior lobe hormones, but dosage with these latter hormones (alpha and beta hypophamine) was earlier

shown (Riddle and Polhemus¹⁹) to cause enlargement in neither the liver nor the thyroid of these animals. The data tabulated here show that these preparations of the gonad-stimulating hormone did not (in any case) cause enlargement of the liver, on the other hand, they did (in every case) produce an enlargement of the thyroid. It would seem therefore that the thyreotropic response is produced by the gonad-stimulating hormone, or by another substance (not growth hormone and not prolactin) with similar solubilities. Further, that the liver enlargement is mediated by the growth hormone, or by a substance (not gonad-stimulating hormone and not prolactin) whose solubilities are similar to those of the growth hormones, or—more probably—by growth hormone admixed with non-physiological and incompatible amounts of another pituitary principle or substance. Possibly the same applies to pituitary-induced glycosuria (Houssay and Biasotti³⁰).

Examining next the data obtained from similar injections of preparations of prolactin (free or nearly free of the gonad-stimulating and growth hormones) we note that this hormone—though producing its normal effect on the crop-glands and lactation—fails to produce significant size-change in either the liver or the thyroid. These data make it improbable that prolactin alone is responsible for either the liver or thyroid enlargement which so commonly follows the injection of extracts of the anterior pituitary.

Members of the medical profession will perhaps have a special interest in the data of table 4. It is here shown that prolan (from pregnant urine) in the form of antuitrin S, and as generously supplied to us by Dr. Oliver Kamm, of the Research Laboratories of Parke, Davis & Co., does not demonstrably affect the size of either the liver or the thyroid in our animals. I believe that the clinical value of this substance is beyond question, that to ascribe to it a pituitary origin is a most hazardous venture, and that to confuse or to associate it with a gonad-stimulating pituitary principle is a serious error.

The additional data given in the lower part of this table show that the commercial product, antuitrin (Parke, Davis & Co.), causes no enlargement of the livers of our animals, it does, however, in all these tests, cause enlargement of their thyroids. It was earlier shown (Riddle and Polhemus¹⁹), and is now confirmed, that fresh samples of antuitrin stimulate testis growth in doves and pigeons. Birds injected with this preparation tend to lose weight, their crop-glands are unaffected, but their gonads grow and their thyroids enlarge. Thus we here again find the thyroid response associated with the gonad-stimulating effect.

SUMMARY

Following the isolation of a third anterior pituitary hormone (prolactin) in fairly pure form, together with the marked advance in the assay and purification of the growth and gonad-stimulating hormone facilitated by this accomplishment, it is perhaps admissible to attempt the association of certain tissue responses with each of the (three) now known hormones of

TABLE IV

Liver and Thyroid and Other Responses of Ring Doves to Other Anterior Pituitary and Pregnant Urine Preparations (Excerpt from Data of Riddle, Bates and Dykshorn)

Preparation	Daily dosage			Body weight		Age	Liver		Thyroid		Crop-gland active (+) or not (-)
Kind	Volume	Mgm	Duration	Start	End		Test	Control	Test	Control (an av)	
			days	grams		mos	grams		milligrams		
Prolan (from urine)	0.2	2.0	5	143	140	3.0	3.88	2.0-4.0	21.6	14.8	—
Antutrin S	0.2	2.0	7	164	159	21.2	4.12		14.1	14.0	—
(095029-B)	0.2	2.0	7	150	148	2.9	3.71		16.8	(21.7)†	—
(Parke, Davis Co.)	0.2	2.0	7	156	147	2.8	2.86		25.7	(21.7)	—
	0.2	2.0	7	147	155	8.0	3.67		13.4	(21.7)	—
	0.2*	2.0	7	132	131	19.2	2.84		18.6	15.6	—
	0.2*	2.0	7	172	162	18.3	3.05		20.7	(22.7)	—
	0.2*	2.0	7	150	145	25.2	4.12		14.5	14.0	—
	0.2*	2.0	7	138	134	19.4	2.60		11.2	(14.3)	—
	0.2	2.0	10	157	140	12.9	5.59		28.0	14.8	—
Antutrin‡	0.2	2.0	4	157	148	2.5	2.23	2.0-4.0	11.9	13.8	—
(Parke, Davis Co.)	0.33	4.5	4	129	121	3.2	2.09		17.3	15.1	—
	0.25	3.5	5	139	136	2.8	3.91		23.1	(14.1)	—
	0.5	7.0	5	145	129	2.6	2.10		21.9	20.3	—
	0.5	7.0	5	154	137	2.7	2.78		33.3	20.0	—
	0.5	7.0	5	150	141	2.9	2.63		42.4	(26.4)	—
	0.33	4.5	9	124	123	2.7	3.31		35.8	20.0	—
	0.33	4.5	9	120	120	2.7	3.62		24.6	(23.0)	—
	0.33	4.5	9	132	132	2.7	2.84		19.6	14.7	—
	0.33	4.5	9	144	141	2.8	4.68		38.2	20.0	—

* These from preparation No 095170-A

† Parentheses indicate control weights which are definitely less reliable than others

‡ Antutrin was earlier shown (Riddle and Polhemus) to contain the gonad-stimulating hormone, this now confirmed

the anterior pituitary. Hitherto, only accelerated body growth was a proved specific response of the growth hormone, and only accelerated gonad growth a proved specific response of the gonad-stimulating hormone.

The recent isolation, identification and assay of a third anterior pituitary hormone by Riddle, Bates and Dykshorn included the demonstration that active milk-secretion in mammals, and the crop-gland response in pigeons are specific responses to this third hormone—prolactin. Some facts essential to that demonstration are here reviewed.

Some data concerning prolactin are given. The "luteinizing substance" obtained from pregnant urine probably does not derive from the anterior pituitary. To associate it with the gonad-stimulating principle of the pituitary is considered a serious error.

Commercial antutrin (Parke, Davis & Co.) is again shown to contain demonstrable amounts of gonad-stimulating (and thyroid-stimulating) hormone.

The enlargement of the liver following the administration of extracts of the anterior pituitary is probably a non-specific, secondary and pathological sequel—illustrating a type of response requiring careful analysis in work with unpurified pituitary extracts. This liver response, like a similarly induced glycosuria, is probably the result of a *functional dysharmony* resulting from the simultaneous presence in the blood—in unusual and non-physiological amounts—of two or more potent anterior principles which never normally thus coexist in the blood.

Hyperplasia of the normally developed thyroid following pituitary administration is a specific response to the gonad-stimulating hormone, or to another anterior pituitary derivative having similar solubilities.

LITERATURE CITED

- 1 EVANS, H M, and LONG, J A Characteristic effect upon growth, oestrous and ovulation induced by the intraperitoneal administration of fresh anterior hypophyseal substance, *Proc Nat Acad Sci*, 1922, **VIII**, 38-39
- 2 SMITH, P E Hastening development of female genital system by daily homoplastic pituitary transplants, *Proc Soc Exper Biol and Med*, 1926, **XXIV**, 131-132
- 3 ZONDEK B, and ASCHHEIM, S Das Hormon des Hypophysenvorderlappens, testobjekt zum Nachweis des Hormons, *Klin Wchnschr*, 1927, **VI**, 248-252
- 4 EVANS, H M, MEYER, K, and SIMPSON, M E Relation of prolactin to the anterior hypophyseal hormones, *Am Jr Physiol* 1932, **c** 141-156
- 5 STRICKER, P, and GRÜTER, F Action du lobe antérieur de l'hypophyse sur la montée laiteuse, *Compt rend Soc de Biol*, 1928, **XCIX**, 1978-1980
- 6 STRICKER, P, and GRÜTER, F Recherches expérimentales sur les fonctions du lobe antérieur de l'hypophyse influence des extraits du lobe antérieur sur l'appareil genital de la lapine et sur la montée laiteuse, *Presse med*, 1929, **XXXVII** 1268-1271
- 7 GRÜTER, F, and STRICKER, P Über die Wirkung eines Hypophysenvorderlappenhormons auf die Auslösung der Milchsekretion, *Klin Wchnschr*, 1929, **VIII**, 2322-2323
- 8 CORNER, G W The hormonal control of lactation non-effect of corpus luteum, positive action of extracts of hypophysis *Am Jr Physiol*, 1930, **xcv**, 43-55
- 9 RIDDLE, O, and BRAUCHER, P F Studies on physiology of reproduction in birds, control of special secretion of the crop-gland in pigeons by an anterior pituitary hormone, *Am Jr Physiol* 1931 **xcvii**, 617-625
- 10 RIDDLE, O, BATES, R W, and DYKSHORN, S W A new hormone of the anterior pituitary, *Proc Soc Exper Biol and Med*, 1932, **XXIX**, 1211-1212
- 11 RIDDLE, O, BATES, R W, and DYKSHORN, S W Prolactin, a new and third hormone of the anterior pituitary, *Anat Rec*, 1932, **liv**, 25
- 12 RIDDLE, O, BATES, R W and DYKSHORN, S W The isolation identification and assay of a third anterior pituitary hormone, *Am Jr Physiol*, 1933 **cv**, (July)
- 13 RIDDLE, O Studies on pituitary functions, *Endocrinology*, 1931, **xv**, 307-314
- 14 FEVOLD, H L, HISAW, F L, and LEONARD, S L The gonad stimulating and the luteinizing hormones of the anterior lobe of the hypophysis, *Am Jr Physiol*, 1931, **xcvii**, 291-301
- 15 SMITH, P E and ENGLE, E T Experimental evidence regarding the rôle of the anterior pituitary in the development and regulation of the genital system, *Am Jr Anat* 1927, **xl**, 159-217
- 16 AILEN, B M Experiments in the transplantation of the hypophysis of adult *Rana pipiens* to tadpoles *Science* 1920, **ns** **liii** 274-276
- 17 SMITH, P E and SMITH, I P Repair and activation of the thyroid in the hypophysectomized tadpole by the parenteral administration of fresh anterior lobe of the bovine hypophysis, *Jr Med Res* 1922 **xliv** 267-283

- 18 RIDDLE, O , and FLEMION, F Studies on physiology of reproduction in birds, the rôle of the anterior pituitary in hastening sexual maturity in ring doves, *Am Jr Physiol*, 1928, lxxxvii, 110-123
- 19 RIDDLE, O , and POLHEMUS, I Studies on physiology of reproduction in birds, effects of anterior pituitary hormones on gonads and other organ weights in the pigeon, *Am Jr Physiol*, 1931, xcvi, 121-130
- 20 PUTNAM, T J , BENEDICT, E B , and TEEL, H M Studies in acromegaly, VIII Experimental canine acromegaly produced by injection of anterior lobe pituitary extract, *Arch Surg*, 1929, xviii, 1708-1736
- 21 LOEB, L , and BASSETT, R B Effect of hormones of anterior pituitary on thyroid gland in the guinea pig, *Proc Soc Exper Biol and Med*, 1929, xxvi, 860-862
- 22 ARON, M Action de la préhypophyse sur la thyroïde chez le cobaye, *Compt rend Soc de Biol*, 1929, cii, 682-684
- 23 SCHOCKAERT, J A A propos de l'action stimulante des extraits préhypophysaires sur la thyroïde, *Compt rend Soc de Biol*, 1930, cv, 223-225
- 24 SMITH, P E , and SMITH, I P The topographical separation in the bovine anterior hypophysis of the principle reacting with the endocrine system from that controlling general body growth, with suggestions as to the cell types elaborating these excretions, *Anat Rec*, 1923, xxv, 150
- 25 EVANS, H M The function of the anterior hypophysis, *The Harvey Lectures*, 1924, Lippincott, Philadelphia, 212
- 26 SMITH, P E Relations of the activity of the pituitary and thyroid glands, *The Harvey Lectures*, 1929-1930, Lippincott, Philadelphia, pp 129-143
- 27 CREW, F A E , and WIESNER, B P On the existence of a fourth hormone, thyreotropic in nature, of the anterior pituitary, *Brit Med Jr*, 1930, i, 777-778
- 28 ARON, M L'hormone préhypophysaire excito-secretrice de la thyroïde Contribution à l'étude du fonctionnement thyroïdien, *Rev franç d'endocrinol*, 1930, viii, 472-520
- 29 LOEB, L The specificity in the action of the anterior pituitary of different mammals as well as of urine of pregnant women on the sex organs and thyroid glands of immature female guinea pigs, *Endocrinology*, 1932, xvi, 129-145
- 30 HOUSSAY, B A , and BIASOTTI, A Hipofisectomia y diabetes pancreatica en el sapo, *Rev Soc argent de Biol*, 1930, vi, 8-24

THE EFFECT OF HORMONES ON CELLULAR PERMEABILITY*

By ERNST GELLHORN, M D , P H D , *Chicago, Illinois*

HORMONE action and nervous action (involving the central and the autonomic nervous systems) are the two important mechanisms of bringing about the adjustment of the organism to its surroundings. Excitatory and inhibitory influences are exerted on the various organs of the body resulting in adaptive coordination. The nervous and the hormone mechanism cooperate, as has been shown for example in Cannon's extensive studies¹. The effects of the discharges of the sympathetic such as occur in rage are enhanced by the liberation of adrenalin. The distribution of the nerves over the whole body and the excitation of large groups of nerves (particularly of the autonomic system) from a small area of the brain make the nervous system an important agency exerting a kind of remote control in the body. In the same way the hormones which circulate in the blood in very minute quantities act to influence various parts of the body in a specific manner. The relationship between nervous and hormone action is known to be still closer since the work of Loewi, Finkleman, Cannon and others (Fryer and Gellhorn²) has shown that the stimulation of autonomic nerves leads to the liberation of chemical substances of hormone characteristics. Acetyl choline and adrenalin must be considered as the vagus and sympathetic substances respectively. (As to the significance of acetyl choline as a hormone consult Le Heux³).

These facts make it probable that the mechanism of nervous and hormone action may be similar in some respects. Now it has been known for some time that nervous stimulation increases the permeability of the cell (compare Gellhorn,⁴ 1929, with bibliography, and Gellhorn and Northup,⁵ 1932) and therefore it is assumed that changes in permeability may play an important part in the regulation of cellular activity. This idea is supported by experiments which show that, in general, permeability decreases reversibly in narcosis. For this reason experiments were carried out to determine (1) whether hormones affect cellular permeability and (2) if permeability changes are specific for different hormones. The latter question seems to be of particular interest from the point of view of the antagonistic action of various hormones.

A recent survey of the literature on this question (Gellhorn⁴) indicated that various observations made on intact organisms were not quite in agreement. Working with the intact organism may lend itself to erroneous

* Paper read before the 17th Annual Clinical Session of the American College of Physicians in Montreal, February 7, 1933. Aided by a grant from the Ella Sachs Plotz Foundation.

From the Department of Physiology, University of Illinois, College of Medicine, Chicago, Illinois

interpretations since uncontrollable changes in circulation may be explained as changes in permeability. Therefore experimental procedures were chosen which permit a more rigid control than do experiments on the intact animal. The first group of experiments was carried out on muscle and skin membranes of the frog.

The muscle membrane made from the abdominal muscles of *Rana temporaria* according to the method of Winterstein⁶ and a sac formed from the skin of the frog according to the method of Wertheimer⁷ were used. Ringer's solution containing sugar was put on one side of the membrane, on the other was a balanced salt solution. The amount of sugar entering the membrane during different periods of time was determined by the Folin-Wu method. Symmetrical membranes from the same frog were regularly used. In preliminary experiments it was found that the permeability of symmetrical membranes from the same frog was under identical conditions about equal. The differences did not exceed 4 per cent in the muscle experiments nor 9 per cent in those on the skin. The average was 2 per cent in the former and 3 per cent in the latter group, so it was certain that differences greater than 10 per cent caused by the application of the internal secretions or of autonomic poisons must be due to a change in the permeability of the membrane.

The principal experiments made by this method showed that the effect of adrenalin on the permeability of the muscle membrane was dependent upon its concentration. If the dilution was 1:1,000,000 the permeability to sugar was increased 21 to 108 per cent. This enormous increase of the permeability was not due to diminution of the irritability, since the internal secretions and the autonomic poisons were always added in such small amounts that no change in the irritability of the membrane occurred. Therefore an increase or decrease in the amount of sugar which entered must have been due to a specific effect on the permeability. Adrenalin in a concentration of 1:5,000,000 caused either an increase or a decrease of permeability, while in still lower concentrations (1:15,000,000) a diminution of the permeability usually occurred. A concentration of 1:50,000,000 was without effect. Corresponding results were obtained on the skin membrane. Here also a regular increase of permeability was found with adrenalin 1:1,000,000, while in lower concentrations (1:5,000,000 and 1:25,000,000) the permeability sometimes increased and sometimes decreased. The sensitivity of the skin was still greater than that of the muscle membrane even in a concentration of 1:50,000,000 adrenalin was observed to cause a decrease of permeability.

Thyroxin caused an increase of the sugar permeability of the muscle membrane in dilutions of 1:100,000 and 1:1,000,000. An increase in the permeability of the skin membrane was found regularly in concentrations of 1:10,000 up to 1:1,000,000. In lower concentrations thyroxin was ineffective.

Finally, corresponding experiments were performed with a preparation

of insulin which was free from disinfectants. It was shown that insulin in concentrations of 1/50 unit per cubic centimeter up to 1/200 unit per cubic centimeter regularly increases the permeability of the muscle membrane, and the same effect was obtained on the skin membrane in concentrations of 1/50 and 1/100 unit per cubic centimeter. In still lower concentrations no effect was obtained. In these experiments also, there was no perceptible change in the irritability. The experiments showed that adrenalin, thyroxin and insulin influence the permeability of a surviving membrane when used in about the same concentrations as those in which they exert their characteristic effects on surviving organs under similar conditions.⁸ Because of the low concentrations in which adrenalin is found in the body it is to be expected that under physiological conditions adrenalin alone decreases the permeability of the cells, while insulin and thyroxin have just the opposite effect. The observations support the conclusions drawn by Eppinger,⁹ Asher and Pfluger,¹⁰ and Wiechmann¹¹ from experiments on warm blooded animals and man after removal of the thyroid and in diabetes mellitus.

TABLE I

Changes in Permeability of Muscle and Skin Membranes Due to Internal Secretions

	Muscle Membrane		Skin Membrane	
	Dilution	Permeability *	Dilution	Permeability *
Adrenalin	1 1,000,000	++	1 1,000,000	++
	1 5,000,000	+ or —	1 5,000,000	+ or —
	1 15,000,000	—	1 50,000,000	—
Thyroxin	1 100,000	++	1 10,000	++
	1 1,000,000	++	1 100,000	++
			1 1,000,000	+
Insulin	1/50 and 1/100 unit per c c	++	1/50 and 1/100 unit per c c	++
	1/200 unit per c c	+		

* + indicates increase, and — decrease in permeability for sugar

Although the results obtained are quite decisive as far as permeability is concerned and also occurred in such low concentrations as to be of physiological significance, it seemed desirable to check and amplify them with a different method in which the physiological state of the preparation was secured by the perfusion method and in which the physiological character of the changes in permeability was proved by its reversibility.

A method devised by Mond¹² was adopted with slight modifications. In a pithed frog the blood vessels supplying the gut, and the gut itself were perfused separately. For perfusion of the capillaries of the gut a cannula was introduced into the celiac artery the gastric branches of which were tied off, preventing perfusion through the stomach and loss of fluid. Through this cannula, by means of a three-way cock, either Ringer's solution or Ringer's solution containing the substance under investigation could be

perfused The liquid, after passing through the gut capillaries, was collected from an outlet cannula introduced into the portal vein

The lumen of the gut was perfused with 3.15 per cent glucose solution through a cannula introduced just posterior to the pylorus, the outlet cannula being just anterior to the rectum

The liquid perfused through the capillaries was divided into samples each of which represented ten minutes of perfusion These samples were analyzed for sugar by the Folin-Wu method

*Results*¹³ Control experiments In order to be certain that changes in the absorption rate, which was used as the indication of permeability, were due to the administration of the substance under investigation, the perfusion rate was kept constant, the perfusing solutions were well oxygenated, and the first few samples were discarded The perfusion was started and finished with Ringer's solution and between those periods Ringer plus hormone was used Complete reversibility of the effects of the hormone added to Ringer's solution was observed in most cases and therefore no difficulties were involved in interpreting these data In other experiments in which, due to high concentrations of the hormones, irreversible effects were obtained, the interpretation of the results could be based on the general course of sugar absorption obtained in control experiments and others in which hormones in subliminal concentrations had been added. It may be emphasized that although in numerous experiments the sugar absorption remained almost equal over a period of two hours, not infrequently a steady decrease in sugar absorption was observed, although all conditions were kept as constant as possible This decrease was most marked in the first periods of the experiments It is very remarkable and indicative of the fact that blood vessels and gut were kept under physiological conditions in this preparation, that in no case was a spontaneous increase in sugar absorption observed in the control experiments Injury is invariably accompanied by an increase in permeability (Compare Gellhorn,⁴ p 195)

Adrenalin In a first group of experiments the effect of adrenalin in concentrations of from 1:500,000 to 1:25,000,000 was studied It was found that adrenalin 1:500,000 to 1:5,000,000 considerably increased sugar absorption (figure 1) It is of interest to note that frequently, as in the curves of figure 1, the effect of adrenalin was greater during the second application The changes in absorption were completely reversible In lower concentrations (1:10,000,000) a decrease in absorption occurred (figure 2) In still lower concentrations (1:25,000,000) the effects were weak Two characteristic examples were given in figure 3, which show that during the first application a slight decrease in absorption was obtained, whereas in the second perfusion period with adrenalin the sugar absorption was slightly increased This again seems to indicate that the adrenalin effectiveness is increased during the second period of its application In our studies not infrequently effects of this type were observed which may be taken as an expression of a cumulative effect upon the cells which allows the sugar to permeate through the gut

The question arises whether the effects on absorption are dependent upon the changes in the diameter of the blood vessels brought about by adrenalin

The results of our experiments show conclusively that no relation exists

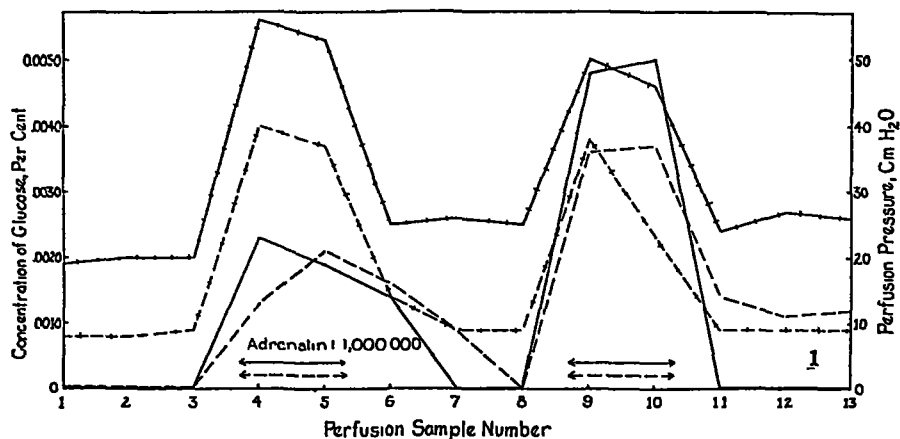


FIG 1 Experiment A (solid line) and experiment B (broken line) with adrenalin 1 1,000,000, which was administered during the collection of the samples covered by the arrows Other samples, perfusion with Ringer's solution

The solid, crossed line shows perfusion pressures for experiment A, the broken, crossed line perfusion pressures for experiment B

between the vasoconstrictor effect of adrenalin and its influence on sugar absorption In concentrations of 1 500,000 to 1 1,000,000 the constrictive effect was very marked and accompanied by an increase in absorption In lower concentrations (compare the curve in figure 2) not the slightest constrictive effect was observed in spite of very considerable changes in

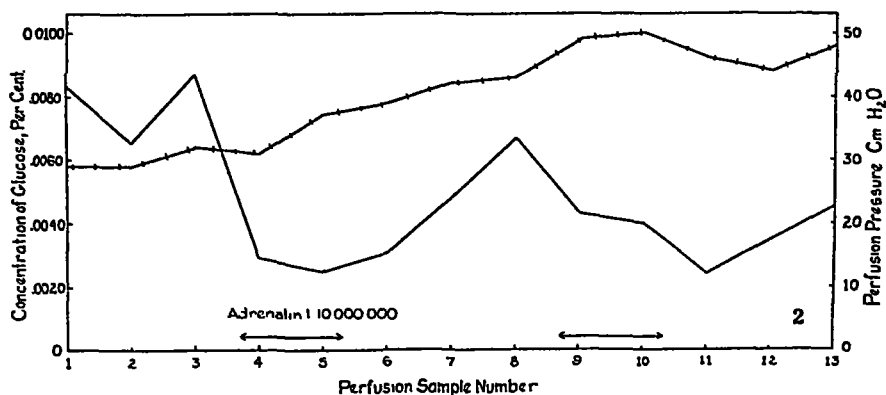


FIG 2 Experiment with adrenalin 1 10,000,000 Details as in figure 1

sugar absorption As was mentioned above, any constrictive effect was at once compensated in order to keep the perfusion rate constant It may therefore be said that independent of its vascular effects adrenalin displays specific effects on the absorption from the gut which depend on the concentration and consist either of an increase or a decrease in absorption

Abderhalden and Gellhorn¹⁴ showed in 1923 that in the presence of small amounts of serum the effectiveness of adrenalin upon the heart is greatly increased. The threshold for the positive inotropic action is lowered and the duration of the adrenalin effect is increased. Therefore the question was investigated whether the action which adrenalin has on absorption may also be enhanced by serum. In our experiments frog serum was used.

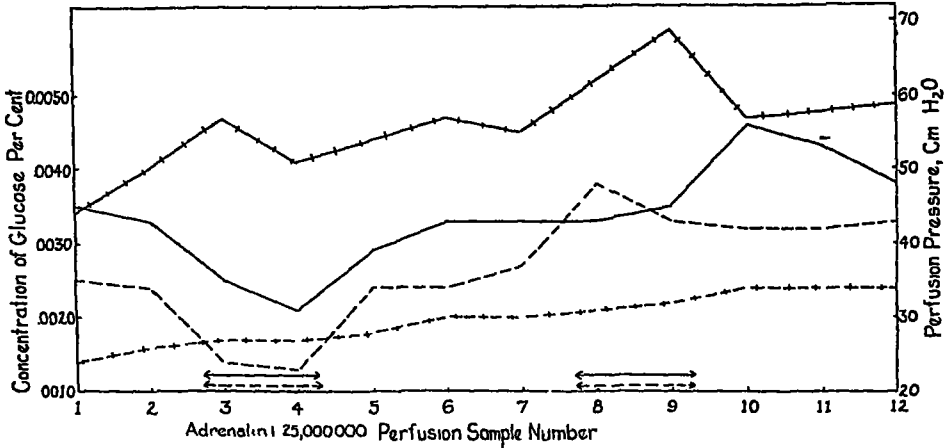


FIG 3 Experiment A (solid line) and experiment B (broken line) with adrenalin 1:25,000,000. Details as in figure 1.

in concentration of 1:500 or 1:5,000 diluted with Ringer's solution. Control experiments showed that frog's serum 1:500 in Ringer alone is without influence on sugar absorption.

Numerous experiments performed with the addition of serum to adrenalin-Ringer in the concentrations mentioned above proved conclusively that adrenalin in such solutions is more effective in influencing sugar absorption than in pure Ringer's solution. In the presence of serum, adrenalin was effective even in a concentration of 1:50,000,000 and increased sugar

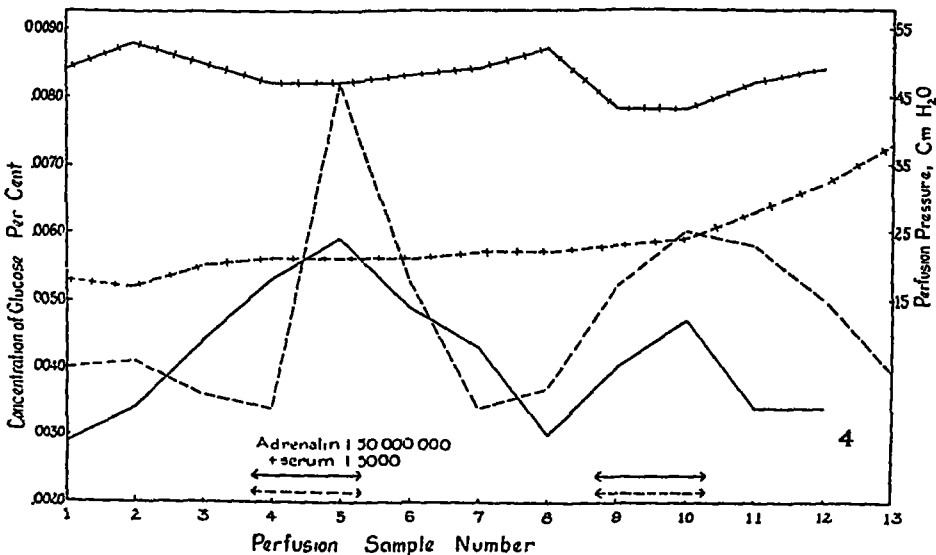


FIG 4 Experiment A (solid line) and experiment B (broken line) with adrenalin 1:50,000,000 plus serum 1:5,000. Details as in figure 1.

absorption reversibly. Such action in the absence of serum requires a concentration of adrenalin of at least 1:5,000,000. These marked effects of adrenalin on absorption were not accompanied by vasoconstriction, as is shown in figure 4.

Thyroxin The experiments with thyroxin were carried out in concentrations of from 1:50,000 to 1:200,000. The pH of Ringer's solution with and without thyroxin was adjusted to the same value ($\text{pH} = 7.6$). The effect in concentrations of 1:50,000 was regularly a marked increase in the absorption of sugar which frequently was more or less irreversible, as shown in experiment A in figure 5. This interpretation is justified,

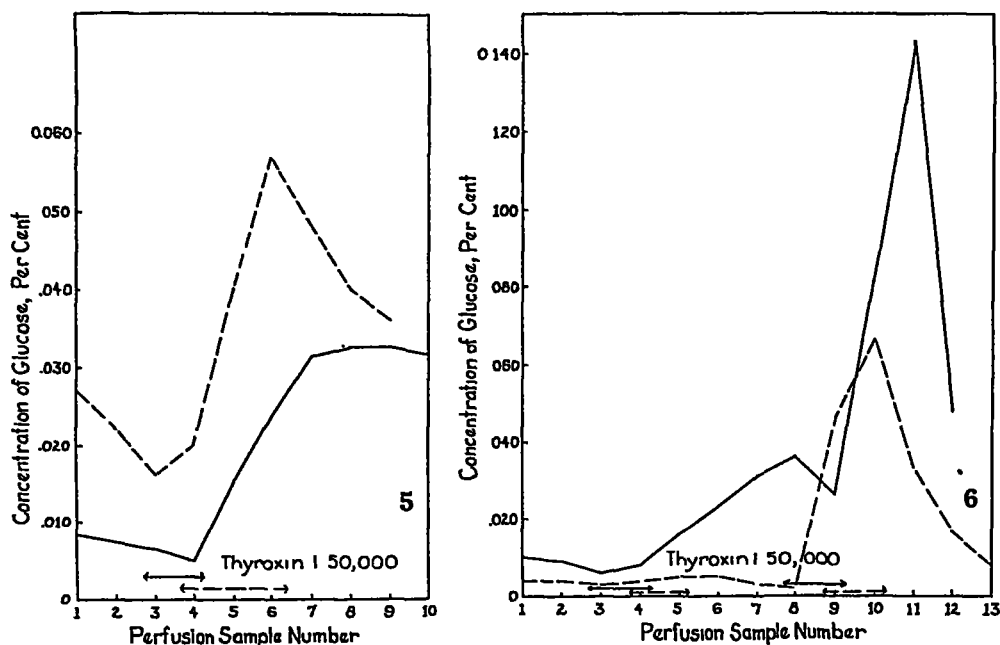


FIG 5 Two experiments, A (solid line) and B (broken line), with thyroxin 1:50,000

FIG 6 Two experiments, A (solid line) and B (broken line), with thyroxin 1:50,000
Graphs of perfusion pressures not given, otherwise details are as in figure 1

since, as was already emphasized, a spontaneous increase in sugar absorption never occurred. Occasionally this increase was delayed, as experiment A in figure 5 indicates. As was shown in the work with adrenalin, an increase in sensitivity to the same drug during its second application was also observed with thyroxin, but to a much greater extent. In fact, it was this group of experiments which called our attention to this phenomenon. Figure 6 gives an example. In both cases the thyroxin effect is very marked during the second application, while it is either completely or almost absent during the first. One also obtains the impression from these experiments that the speed with which the reaction is brought about is greater during the second than during the first application of the drug. That is particularly distinct in experiment A, in which the increase in sugar absorption occurred with very great delay during the first part of the experiment but

much faster in the second period, although even here after the perfusion with thyroxin

It is significant that thyroxin never influenced the perfusion rate. In the concentrations mentioned above it was without influence on the capillaries, causing neither contraction nor dilatation.

In concentrations of 1:100,000 an increase in sugar absorption was also observed. In this concentration there was again a characteristic increase in sensitivity in the second application of thyroxin. Frequently the first application was without effect, while the second caused a marked increase in sugar absorption. This increase was characteristically delayed, occurring after the perfusion with thyroxin was over.

Only a slight increase in sugar absorption occurred in experiments with thyroxin 1:200,000. Still lower concentrations were not examined.

Another series of thyroxin experiments was performed in the presence of a serum (frog's serum 1:500 in Ringer's solution). Neither the type nor the range of concentrations in which thyroxin was effective was changed.

Insulin. A preparation from Lilly (Iletin) was used. Since it contains 0.2 per cent phenol, corresponding amounts of phenol were added to Ringer's solution so that it differed from insulin-Ringer only by its insulin content. Insulin was examined in concentrations of from 0.02 to 0.0033

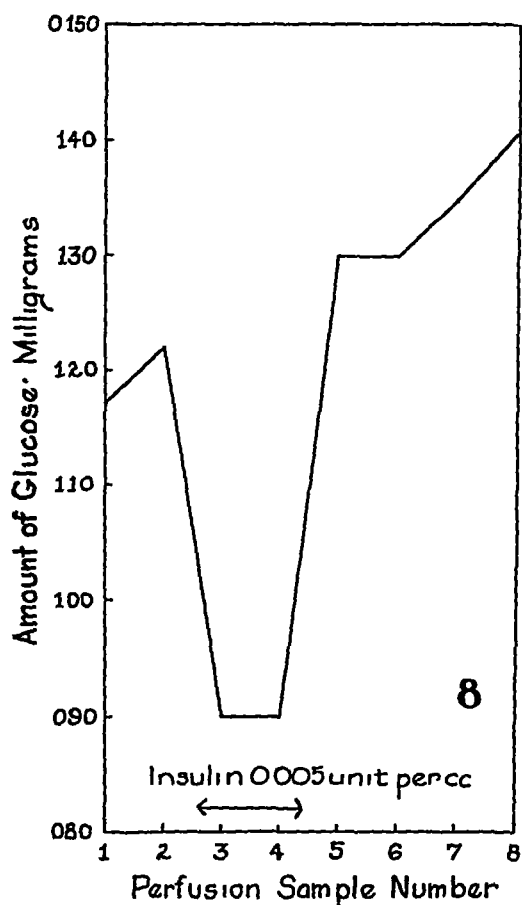
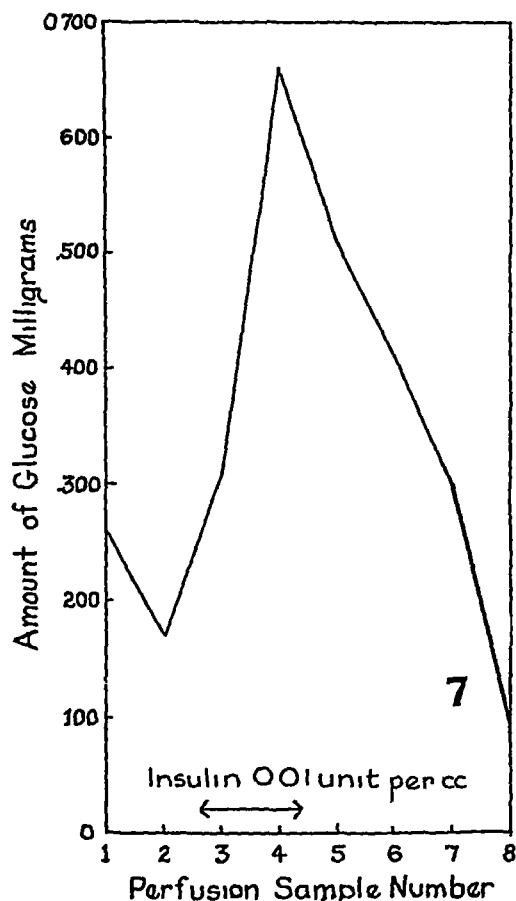


FIG 7 Experiment with insulin, 0.01 unit per cubic centimeter Details as in figure 5
 FIG 8 Experiment with insulin, 0.005 unit per cubic centimeter Details as in figure 5

units per cubic centimeter Figure 7 shows that insulin in a concentration of 0.01 unit per cubic centimeter increases absorption. With 0.02 unit per cubic centimeter the effect is the same, but it is frequently irreversible. Occasionally a delayed effect was observed, i.e., the greatest increase in sugar absorption occurred in the Ringer periods which followed the application of insulin. Five-thousandths unit per cubic centimeter decreased reversibly the absorption of sugar, as shown in figure 8, but 0.0033 unit per cubic centimeter was without any effect. In these experiments the question was also investigated whether the addition of small amounts of serum as used in the previously described experiments had any influence on the insulin effect. The result was a distinct decrease in the insulin effect in the presence of serum.

As in the thyroxin experiment, the perfusion rate remained unchanged in the insulin periods. Therefore the insulin influence on sugar absorption cannot depend on vascular effects.

Hormones of the Hypophysis A great many experiments were performed with the hormones of the hypophysis. We used pituitrin (Parke Davis and Company) and powderized dried gland of the posterior hypophysis in concentrations ranging from 1 to 40 units per liter. There was no effect on the permeability of the gut to glucose, the concentration of the latter remaining either unchanged in the blood vessels or showing a slight gradual decrease as was observed in control experiments without the addition of a hormone. But it seems worth while mentioning that the hormone has a distinct effect on the blood vessels supplying the gut. They showed a marked constriction while the hormone of the posterior hypophysis was flowing through the blood vessels and this is indicated in figure 9, by the rise in pressure which was necessary to maintain the same output. The effect is quite

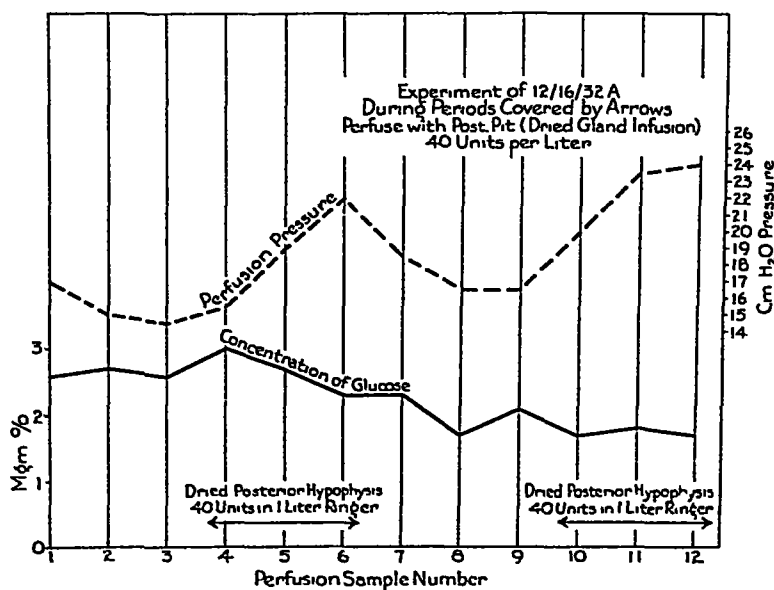


FIG 9 Experiment with dried posterior hypophysis 40 units per liter

reversible These experiments emphasize again that there is no relationship between the effects of a substance on blood vessels and on permeability. Thyroxin and insulin showed profound effects on permeability without influencing the blood vessels at all, the adienalin effects on permeability were not in proportion to the degree of vasoconstriction and the observations with posterior hypophysis show vasoconstriction without permeability changes

Since in absorption experiments on intact animals a distinct retardation in absorption was observed by Thienes and Hockett¹⁸ after administration of extracts of the posterior hypophysis it must be concluded that this change in absorption is not due to an alteration in permeability but simply to a vascular effect Just this example may be a good illustration of how necessary it is to control rigidly the circulatory conditions if an analysis of a drug or hormone effect in regard to permeability is desired

A careful study of the effects of antuitrin (Parke, Davis and Company) on absorption of sugar in concentrations of from 1:125 to 1:1000 was completely negative Referred to the concentrations of fresh anterior lobe of the hypophysis the concentrations are 0.96 per cent to 0.12 per cent There were also no effects either on the blood vessels or on the gut

Acetyl Choline The experiments with acetyl choline were carried out under the same conditions, and concentrations varying between 1:50,000 and 1:40,000,000 were used The results are very striking and are essentially different in high and low concentrations In the first case (figure 10)

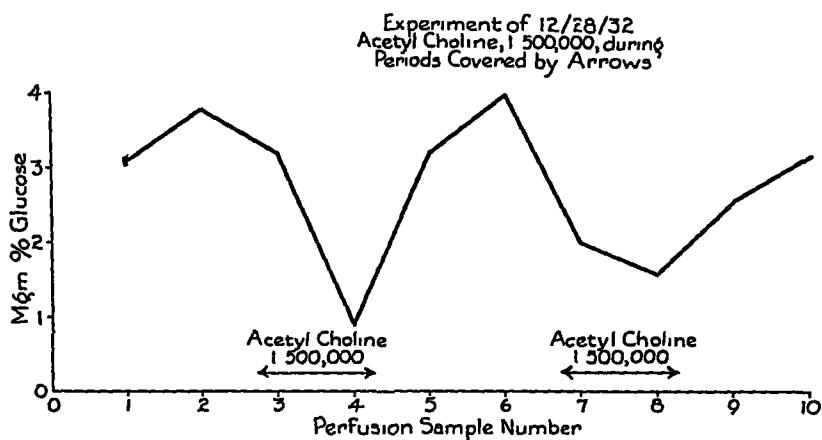


FIG 10 Experiment with acetyl choline 1:500,000

a decrease in sugar absorption invariably occurs, whereas in low concentrations the absorption of glucose increases The latter effect is weaker than the first Both effects are reversible

These experiments are particularly interesting in comparison with the results obtained with adrenalin The antagonism between the sympathetic hormone adrenalin and the parasympathetic hormone acetyl choline is quite evident Low concentrations of adrenalin, such as may be of physiological significance, decrease permeability, whereas acetyl choline increases it In high concentrations the same antagonism obtains since adrenalin increases

permeability, whereas acetyl choline lowers it. The frequently stated antagonism between the sympathetic and parasympathetic nervous systems which also can be demonstrated, as is well known, by the study of drugs which stimulate the sympathetic and vagus respectively, holds true as our experiments prove in reference to permeability (Gellhorn and Northrup¹⁶)

Discussion The experiments described in this paper show conclusively that hormones influence permeability in a specific manner. The effects are practically identical in muscle and skin membranes, and in the gut wall. They occur in concentrations similar to those in which these substances produce well known effects on heart, blood vessels, metabolism, etc. It may therefore be said that the permeability effects described in this paper are equally significant from a physiological point of view. That is to say, the results are not simply of pharmacological interest.

Concerning the influence of hormones on absorption, ample experimental evidence is given that the effects are independent of changes in the diameter of the blood vessels. It is not quite clear as yet whether or not changes in permeability of capillaries are at least partially responsible for the changes in absorption which were obtained under the influence of different hormones. But it may be said that substances which affect the bore of capillaries and arterioles markedly do not necessarily change their permeability provided that the alteration in circulation is compensated by appropriate changes in perfusion pressure.

Summary Experiments on muscle and skin membranes and on the gut were carried out in order to determine the influence of hormones on permeability under well controlled conditions. It was found that adrenalin, thyroxin, and insulin increase permeability in relatively high concentrations, a decrease in permeability was caused by low concentrations of adrenalin and insulin. Small concentrations of serum increase the effect of adrenalin and diminish that of insulin.

Acetyl choline behaves as an antagonist of adrenalin in regard to permeability.

The hypophysis hormones are without effect on permeability.

The permeability effects of hormones are independent of changes in the diameter of capillaries and arterioles which they may produce.

The physiological character of the experiments is evident (1) from the reversibility of the permeability changes, and (2) from the fact that the changes in permeability occur in concentrations similar to those which affect heart, blood vessels, and metabolism.

REFERENCES

- 1 CANNON, W. B. Bodily changes in pain, hunger, fear and rage, 2 Ed., 1929, D. Appleton, New York.
- 2 FRYER, A. L., and GELLHORN, E. On the principle of autonomic nervous action, *Am. Jr. Physiol.*, 1933, **III**, 392-399.
- 3 LE HEUVE, T. W. Cholin als Hormon der Darmbewegung, *Pflügers Arch.*, 1919, **CLXXIII**, 8-27.

- 4 GELLHORN, E Das Permeabilitätsproblem, seine physiologische und allgemein-pathologische Bedeutung Bd 16—Monographien aus dem Gesamtgebiet der Physiologie der Pflanzen und der Tiere Herausgegeben von M Gildemeister, und anderen, 1929, J Springer, Berlin
- 5 GELLHORN, E, and NORTHUP, D Does physiological excitation influence permeability in striated muscle?, *Am Jr Physiol*, 1932, c, 173-177
- 6 WINTERSTEIN, H Narkose und Permeabilität, *Biochem Ztschr*, 1916, lxxv, 71-100
- 7 WERTHEIMER, E Über irreziproke Permeabilität, *Pflugers Arch*, 1923, clxxix, 383-401
- 8 GELLHORN, E, and GELLHORN, H Über den Einfluss von Hormonen und vegetativen Giften auf die Permeabilität tierischer Membranen, *Pflugers Arch*, 1928, ccxxi, 247-263
- 9 EFFINGER, H Zur Pathologie und Therapie des menschlichen Oedems, 1917, J Springer, Berlin
- 10 ASHER, L, and PFLUGER, O Nachweis der Abhängigkeit der Schilddrüsenfunction vom Zentralnervensystem, *Ztschr f Biol*, 1927, lxxxvii, 115-128
- 11 WIECHMANN, E Zur Permeabilitätstheorie des Diabetes mellitus, *Deutsch Arch f klin Med*, 1926, cl, 186-207
- 12 MOND, R Untersuchungen am isolierten Dunndarm des Frosches, *Pflugers Arch*, 1924, ccvi, 172-193
- 13 GELLHORN, E, and NORTHUP, D Quantitative investigations on the influence of hormones on absorption, *Am Jr Physiol*, 1933, ciii, 382-391
- 14 ABDERHALDEN, E, and GELLHORN, E Weitere Versuche zur Kenntnis der Adrenalinwirkung, *Pflugers Arch*, 1923, cxcix, 437-456
- 15 THIENES, C H, and HOCKETT, A T Decreased absorption from the alimentary tract following injection of posterior pituitary extract, *Jr Lab and Clin Med*, 1931, xvi, 843-849
- 16 GELLHORN, E, and NORTHUP, D Unpublished experiments

UNDERNUTRITION AND ITS TREATMENT BY ADEQUATE DIET*

By J M STRANG, M D , and F A EVANS, M D , F A C P ,

Pittsburgh, Pennsylvania

THE DEFINITION of the state of undernutrition is of necessity somewhat arbitrary. Although occasional reference is seen to absolute weight deficiencies, the usual practice is to consider the weight deficit with reference to other personal statistics. The theoretically ideal weight for a given age, sex, and height may be obtained from many statistical studies⁵⁶. A deviation of over 10 to 15 per cent below an ideal weight may be regarded as undernutrition^{15, 48}. In our series we have arbitrarily set 15 per cent as the critical level. We have not attempted the intricate differential diagnosis between undernutrition and simple underweight⁵.

The condition may be acute or chronic. In acute undernutrition it is usually conceded that the weight loss has a direct relation to a period of inadequate food intake. Chronic undernutrition on the other hand is regarded as a new type of phenomenon for which an explanation must be sought. The hypotheses which have been advanced in the literature may be grouped into those which postulate (1) anomalies of metabolism, (2) unusual conditions of the endocrine glands or (3) peculiarities of the nervous system, especially the basal centers. A careful review of the available literature fails, in our opinion, to support adequately any of these proposed explanations. In contrast to these conceptions, the principle may be expressed that chronic undernutrition, like acute undernutrition, is always the result of a dietary inadequacy. The reasons why the diet is inadequate may vary in chronic states just as they do in acute conditions. On the basis of this assumption a number of patients suffering from undernutrition both of the acute and chronic forms have been treated by dietary measures. The present report summarizes our experience with this method of treatment over a period of four years.

FACTORS PRODUCING UNDERNUTRITION

In the present consideration of undernutrition, the attention is focused upon the non-specific forms. It is recognized that certain accessory food substances are required to prevent scurvy, pellagra, beri-beri etc. These fully developed conditions due to vitamin deficiency are relatively rare in our modern conditions of life, although some of the less dramatic forms of undernutrition may possibly be associated with relatively low vitamin intakes^{25, 45, 60}.

The dietary protein is again a matter of great importance. The qualita-

* Received for publication November 11, 1932. From the Medical Service of the Western Pennsylvania Hospital.

tive variations in the common food proteins have been long recognized^{32, 15} In practice the purely quantitative aspects are perhaps of more immediate importance⁴⁷ The serious effects of prolonged lack of protein intake have been reviewed by Lusk³³ In certain types of undernutrition low plasma proteins⁴⁶ and edema^{52, 65} are probably associated with subminimal protein intake It is also important to recognize that the minimum protein intake is not necessarily the optimum protein intake^{9, 41, 53, 58}

The importance of heredity as an etiologic factor in undernutrition has been subject to considerable discussion Some authors regard leanness as a deeply seated constitutional tendency which is quite unaffected by increased feeding^{37, 66} There exists, however, a belief that although undoubtedly heredity influences certain special characteristics of the individual, the nutritional state is more directly the result of his environment Hereditary phenomena may perhaps be considered as relatively more conspicuous in infants and young children Hence the increased significance of the statement by Holt,¹⁵ "The second group, in which malnutrition is an acquired condition, is the larger one The principal causes are ignorance or neglect of the common rules of hygiene, the observance of which is essential to normal healthy growth" In dealing with adults the point may be made that what is often considered hereditary influence is in reality the result of environment in the form of a family custom of inadequate feeding which becomes fixed in childhood and persists as faulty eating habits through adolescence to maturity

Endogenous thinness or undernutrition due to an endocrine disorder is a conception which has a popular appeal Many authors are somewhat vague as to the exact significance of the term, endogenous undernutrition By definition and as specifically stated by certain writers, this condition means a thin state which results from a dysfunction of one or more endocrine glands The implication necessarily exists, and in some papers the statement is made, that this effect is produced by an endocrine imbalance regardless of food supply From this point of view undernutrition has been described as the resultant of an imbalance of the endocrine glands as a group or as the resultant of defects of certain specific glands^{23, 30, 31, 50, 63} In practice the identification of these specific types of undernutrition on the basis of either metabolic or anthropometric evidence^{23, 63} would be a matter of considerable difficulty

It is perhaps only natural that leanness should be attributed to abnormal function of the thyroid gland Although a loss of weight frequently parallels an abnormally high level of metabolism, undernutrition as part of a hyperthyroid state is not included by most authors in the category of endocrine undernutrition A variety of endocrine undernutrition which is associated with a hypothyroid state has been reported A characteristic fat distribution for this state has been described⁶⁸ although most authors appear to have made the diagnosis on the basis of the metabolic data⁶⁴ A low basal metabolism is generally recognized as present in chronic thin states^{10, 42}

It may definitely be questioned, however, whether this low metabolism is a result of hypofunction of the thyroid gland^{22, 44} Thyroid extract has been given to many undernourished patients to elevate the metabolic level^{3, 44, 64} The clinical response did not parallel the increase of metabolism^{3, 64} although a number of patients experienced a definite increase in appetite

The relation of undernutrition to dysfunction of the pituitary gland has been enthusiastically advocated Here again the identification of the clinical type from either the anthropometric⁶⁸ or the metabolic data¹⁸ is difficult Frequent reference is seen to Simmonds' hypophyseal cachexia^{6, 10, 50, 51, 66} as a severe form of emaciation resulting from hypophyseal disease The advanced condition is rare, but it has been suggested that milder forms of pituitary leanness may be more common⁶⁶ There is, however, considerable reason to question the etiologic relationship between hypophyseal disease and severe undernutrition^{3, 19}

The possibility that a functional insufficiency of the pancreas, especially of the islands of Langerhans, may act as a cause of undernutrition has been suggested¹³ This conception has resulted in an extensive literature relative to the use of insulin in the treatment of chronic thin states These reports appear to agree regarding the beneficial results of insulin therapy There are, however, two distinct schools of opinion as to the mechanism whereby this improvement is brought about One group of investigators feels that insulin promotes a readjustment of certain factors of the cell metabolism whereby a gain in weight is permitted The second school attributes the weight gain and the clinical improvement to the increase in food intake which results from the improvement in appetite due to the use of insulin The views of the first group are summarized in the discussion of Metz³⁸ The report of Short⁵⁷ is perhaps typical of those who feel that the principal influence of insulin is upon the appetite He emphasized the fact that when patients can be induced to eat, the improvement is rapid In addition to the animal experimentation of Macleod³⁵ a number of careful clinical studies have been reported^{1, 4} This evidence appears to indicate that insulin greatly stimulates the appetite, thus promoting the ingestion of large quantities of food and thereby the increase of weight

The coexistence of endocrine disorders and undernutrition may not be doubted In reviewing the conceptions regarding the relation of the endocrine glands individually or as a whole, to undernutrition three points must be kept in mind (1) the criteria which are used as indices of endocrine gland malfunction, (2) the possibility that an observed abnormality of endocrine gland function might be the result of the undernutrition and (3) the probability that the relation of specific endocrine disease to an existing undernutrition is concomitant rather than causal

The diagnosis of specific endocrine types of undernutrition is impeded by the paucity throughout the literature of descriptions which permit the identification of the several specific types Those criteria which exist^{1c, 63} are somewhat difficult of practical application The use of the basal meta-

bolic level as an index of thyroid function alone has repeatedly been questioned^{24, 44} Furthermore, alterations of the specific dynamic action of food³⁶ are not reliable diagnostic aids in endocrine disorders³⁴ and specifically not so in disorders of the pituitary gland^{23, 34, 40, 61}

The evidence that endocrine disorders may result from undernutrition is abundant^{2, 18, 33, 50} The studies of starvation which have been reviewed at length by Lusk³³ afford many illustrations Chronic undernutrition frequently results in amenorrhea in the female³³ The effect on the male has been indirectly shown by loss of libido and sexual power³⁹ The anatomic changes in certain endocrine glands as a result of undernutrition have been described in great detail^{17, 28, 29, 59} The effect of the war upon the incidence of endocrine disease¹² has repeatedly been mentioned Perhaps the most spectacular evidence is cited in the work of Stefko⁵⁹ who described his observations in Russia His conclusion that underfeeding causes endocrine disturbance is quite convincing From another point of view it may be urged that normal cell function is dependent upon an adequate food supply The effect of lack of iodine on thyroid function is well known The close chemical relationship of certain hormones to specific amino acids and the possibility of their derivation from these acids¹² emphasize the importance of the supply of food proteins

When proved endocrine disease is found in association with incipient or fully developed undernutrition, it does not necessarily follow that the undernutrition is a direct consequence of the glandular disorder The undernutrition is rather the result of the failure of the food intake to approximate the daily energy requirements Perhaps the clearest illustration of this fact is provided by the work of Shelling⁵⁵ on parathyroidectomized rats It was definitely shown that the test animals became emaciated as a result of a failure to eat and regained the lost weight promptly when the food intake was resumed The reason why the animals would not eat certain foods appeared to be related to the glandular dysfunction However, if a diet qualitatively proper was provided, the undernutrition disappeared Clinically this identical phenomenon has been observed in thyroid disease and in pituitary disease The disease may continue unrelieved but the nutritional state may be altered by proper feeding This point will be further elaborated in the discussion of energy balance

Closely related to the conceptions relative to the endocrine regulation of undernutrition are those which postulate a disturbance in function of the central nervous system as the etiologic factor The most common opinion states that centers exist in the mid-brain which specifically regulate metabolism regardless of food intake^{10, 66} The intervention of the sympathetic nervous system in the metabolism of food has also been described^{11, 27}

Again, as in the case of the endocrine apparatus, there is no question as to the coexistence of disorders of the nervous system and of undernutrition The contrasting point of view states that the abnormalities of the nervous system are frequently secondary rather than primary The development of

instability of personality has been repeatedly described in starvation^{32, 33} and the lesser degrees of undernutrition.² The effect of undernutrition on the sympathetic nervous system and particularly the functioning of the vagus nerve has been reviewed by Levine.²⁵ Severe forms of nervous disorder are more frequently identified with the specific undernutrition associated with avitaminosis.¹⁴ The dementia of pellagra is well known as are the lesions of the nervous system due to the absence of vitamin B. The cord degeneration of pernicious anemia may also be mentioned. In the very serious form of undernutrition, "anorexia nervosa," the close relationship of undernutrition and central nervous system function is well recognized.^{3, 44, 50} When this advanced stage is reached, it is not always easy to determine causality.

The importance of the energy balance as a factor in the development of undernutrition has been much debated. After the discovery of vitamins there was a tendency to minimize the energy factors. The increase in knowledge regarding the autonomic nervous system has also shown new potential regulatory mechanisms. Certain discussions of these phenomena convey the impression that these factors are of primary importance.^{7, 30, 66} There is no doubt that the endocrine glands, the accessory food substances, and the autonomic nervous system may influence the intermediate metabolism of many specific types of food. There is also no doubt that these influences cannot initiate the supply of necessary material. It is, moreover, a fair criticism of certain of the published case histories of alleged endocrine or medullary undernutrition that the patients were not adequately fed during the periods of observation.

Caloric intake is determinable with relative ease and a few observations have been made of the relation of food intake alone to weight changes.^{20, 43}

The absence of a reliable method of clinical application for the determination of total caloric output is one of the chief obstacles to the absolute proof of the preëminence of energy balance in nutritional states. Apart from observations of basal metabolism and specific dynamic action, the caloric output can rarely be approximated. The variations in energy expenditure that occur during periods of work, and of work-free time, and the great variability of personal habits make an estimation of output under normal conditions quite unreliable.^{21, 26, 54} The endocrine or hereditary etiologies of leanness postulate undefined abnormalities of energy output.³⁷ High energy outputs are readily recognized in thyrotoxicosis and fever, the two conditions in which rapid and spectacular weight changes are obviously attributable to energy deficiency. In the more chronic forms of undernutrition, numerous investigations have failed to reveal any abnormal increase in output. The existence of an abnormality of specific dynamic action in association with undernutrition³⁶ has been questioned^{23, 61} and the etiologic importance of a possible small variation in this factor may be regarded as very slight.^{10, 47, 61} The basal metabolism is uniformly reported as normal or low. Furthermore, the reduction in the body mass which must be trans-

ported, and the inactivity due to semi-invalidism further reduce energy output. The total energy output in chronic undernutrition is, therefore, much diminished as compared with health.

In discussions of energy relations emphasis must not be placed upon the intake or the output of energy but upon the energy balance. Except in conditions of constant true weight balance, the caloric intake in no way reflects the caloric output.⁴⁰ Given a negative caloric balance, the weight loss is determined by two factors: (1) the magnitude of the negative balance, which defines the rate of change and (2) time, which defines the total change. It is general experience that acute illness is almost uniformly accompanied by a fickle appetite and consequent low food intake. The combination of lowered intake and elevated output exaggerates the energy deficit and produces an appreciable rate of weight loss. In more protracted illness, with the exception of a few conditions like thyrotoxicosis, the same fickle appetite prevails. Here, however, the output of energy is much diminished. The negative energy balance is due almost entirely to the diminished intake.²³ The rate of weight loss is small. The time factor then becomes of great importance in the determination of the total weight loss.

However, in neither acute illness nor in chronic illness is a weight loss an inevitable consequence of the disease. In acute febrile states no weight loss occurs if the food intake is forced up to cover the excessive output as was first demonstrated by Coleman and DuBois⁸ in typhoid fever. Likewise, in thyrotoxicosis, no weight loss develops if the intake is adequate (patient 18 and other unpublished cases of our series). In the more protracted illnesses, weight loss may be checked or weight may be gained by forcing up the energy intake as Berkman³ and others^{1, 44} have done in advanced cases of anorexia nervosa and Riecker and Curtis⁵¹ in the marked undernutrition associated with Simmonds' disease. These results have been further emphasized by Shelling⁵⁵ in his work on experimentally produced cachexia parathyreopriva.

Thus there appears to be no more fundamental difference between the acute and chronic types of process than that of rate of development. The frequently mentioned "exogenous" undernutrition may perhaps be called "acute" undernutrition whereas the "endogenous" may be called chronic undernutrition. The characteristic which is common to people who have lost large amounts of weight is that they have lived long enough after the onset of disease, be it mental such as dementia praecox, neoplastic such as cancer of the stomach or adenoma of the pituitary gland, or infectious such as tuberculosis or an intractable pyelitis, to have suffered a significant total weight loss. The development of secondary disturbances of the several endocrine glands, of the nervous system, or of other corporeal systems as a result of the prolonged undernutrition often obscures the primary etiologic factor in the clinical picture which it presents. When, as frequently occurs, the background for chronic undernutrition is laid during the growth period

of childhood or adolescence, certain anatomical changes are to be expected in all organs including the endocrine glands. When the period of underfeeding begins after maturity, both the anatomic and physiologic abnormalities resulting therefrom may be less conspicuous.

PRINCIPLES OF TREATMENT

The basic principle which was followed in the treatment of these patients is that, given a general mixed diet with no specific food deficiencies, the intake must exceed the output in order to produce a gain in weight. The rate of gain in weight is determined by the amount by which the intake exceeds the output. The total gain in weight is determined by the rate of gain and by the duration of the period of treatment.

The amount of food which ordinarily must be ingested in each twenty-four hour period in order to secure a reasonable rate of weight gain was found to be 3000 to 3500 calories. The criteria which have been advocated for the estimation of the desired intake from the kilograms of body weight appeared to us to be unnecessary. If they are employed, 65 to 75, or even 90 calories, per kilogram of actual weight should be given. On the basis of ideal weight, these values become proportionately less. The exact level of intake is determined primarily by the rate of weight gain desired. Not all patients were able to ingest the full diet at once. In special cases, we have used diets of 2200 to 2500 calories for three to four days. In practically all cases it was a simple matter to step up the intake to 3500 calories after a week or two on a 3000 calorie diet. A 3500 calorie diet produced an adequate rate of gain in the ordinary case. Higher levels have been used on special cases, the maximum for our series being 5100 to 5300 calories.

The distribution of these relatively large food quantities into meals is of considerable importance. In the hospital series, the total daily intake was divided into approximately equal calorie meals. Intermediate feedings were the rule in the office patients and were generally successful. Great stress was laid upon regularity in eating habits in connection with the training of the gastrointestinal tract to its new duties. A large number of the patients habitually had eaten one or, at most, two adequate meals per day. In most cases breakfast was the meal which was slighted or omitted. The reëducation of patients in this single respect is a long step toward improvement. In order to permit the stomach to empty before the noon meal, breakfast must be eaten early in the morning. In the hospital the meals were served at 7:30, 11:30 and 4:30. In the office practice, we encouraged our patients to get up early enough so that they could eat a proper breakfast.

The type of food which was employed in these diets was considered as of less importance than the caloric value. There were, however, certain factors which required specific attention. The protein intake was usually set at one gram per kilogram of ideal weight, which corresponded to 50 to 70 grams. On the basis of actual weight the proportion varied between

1.3 to 1.5 grams per kilogram. As will be shown later in the studies of nitrogen balance, this supply of protein covered the daily need with ample residue for storage. Occasionally the protein intake was raised to 90 to 100 grams when a peculiar reason appeared to exist. These higher levels usually accompanied the very high intakes such as 4500 to 5000 calories. The adequacy of the protein, that is, its biological value, was secured by the liberal use of beef, milk, eggs and similar substances of animal origin although a fair amount (30 to 40 per cent of the protein) was often given in the less complete vegetable proteins. Due care was also taken to insure an adequate supply of the vitamins and salts. The liberal use of fresh vegetables, butter, milk and eggs undoubtedly more than covered the daily need. Cod-liver oil, viosterol, yeast, wheat germ preparations and other concentrated vitamin preparations have been used at times without perceptible influence on the general course of events.

Our series showed that patients will gain weight on high fat diets or on high carbohydrate diets. Diets with fatty-acid-glucose ratios varying from 5 to 3.2 have been used and adequately handled by the body. The problem of potential acidosis with the higher ratios has not appeared to be important in our series. The advantage of the high fat diets was the small bulk, the disadvantages were the high satiety value and the prolonged stomach emptying time. High fat diets were harder to follow for any prolonged period of time. The high carbohydrate diets were distinctly more palatable and contained the types of food to which the average patient is accustomed. The large volume occupied by these foods was a handicap to many patients. However, in addition to the greater palatability of these lower energy foods, there is perhaps a definite advantage to be derived by the systematic mechanical distension of the stomach and intestines which is secured by diets of moderate bulk.

Since the present thesis requires a positive energy balance for the gain of weight, we must consider also the output of energy. The basal metabolism in the majority of patients was low, although not abnormally low for the actual mass of the patient. The extrabasal energy output may be divided into the heat of specific dynamic action, the work energy and the non-work fraction. It is obvious that since the specific dynamic action varies with the food intake, an increase in output from this source is inseparable from an increase in energy intake. This extra heat loss, however, does *not* approximate quantitatively the extra energy taken in. The work fraction in most cases may be sharply reduced. Often 500 to 1000 calories a day may be saved. The energy loss from other sources, not work, is very hard to estimate because of the difficulty in analysis of individual habits. In two respects great savings in energy output of this nature may be secured. During 12 to 14 hours a day this factor may be minimized by requiring absolute rest in bed. In addition to the nine or more hours rest each night, rest periods were required for an hour after each meal. The importance of post-prandial rest periods cannot be over-

emphasized and we consider them one of the most valuable items of the regime. They are of benefit not only in that they increase the total daily rest from 20 to 30 per cent but also they are of particular value in promoting rest at times when the physiological reserves of the body, especially of the circulatory organs, are subject to the increased strains consequent upon food handling. The second economy may be effected by a reduction of the purely waste energy resulting from the thousands of purposeless movements which are so commonly noted in thin subjects. Liberal doses of bromides were of great assistance in reducing muscle tension, fidgeting, and purposeless movements.

In summary we may review the most important factors in the energy balance. The energy intake may be raised to 3000 to 3500 calories. This often means an increase of 1000 to 1500 calories over previous levels. With reference to energy output, no economies can be expected in either the basal fraction or the specific dynamic action fraction. In fact both factors tend to increase somewhat. The greatest single potential energy saving lies in the elimination of 500 to 1000 calories of the work fraction. The portion of the non-work, extra-basal energy which may be spared cannot be determined but perhaps may reach a few hundred calories. From these approximations, it may be seen how it is possible to create a positive energy balance of sufficient proportions to permit a reasonable rate of weight gain.

From the practical standpoint, there are certain important economic aspects to dietary procedures. Two of the chief factors in this respect are (1) cost of food and (2) the economic status which permits adherence to the specific routine. Contrary to expectation, high caloric diets are not necessarily inordinately expensive. It was found that the total cost of the various foods which form the back-bone of high caloric menus, such as meat, cream, butter, and bread, was, in the amounts eaten, much less than that of the fruits and vegetables in the same diet. The second economic factor consists of the requirement that the patient be able to adhere to the specific routine which is demanded. It is our practice to insist that nothing in the patient's routine must interfere with the schedule. It is, in our opinion, impossible properly to treat a serious case of undernutrition while the patient continues at work.

In undernutrition, psychic influences are of considerable importance especially because of their effects upon appetite. Two important factors of this type center around the environment and the food supply. An environment which produces frequent emotional crises is incompatible with successful treatment. These environmental difficulties often take the form of over-solicitous parents or relatives. One of the most significant advantages of institutional treatment lies in the endless routine cycle of food, rest, and visits. In non-institutional patients a similar "low-grade" daily routine can be devised. It is in regard to the food itself that the worst psychic handicaps are usually encountered. Many undernourished patients

have long lists of specific food repulsions. After reasonable cooperation on the part of the cook or dietician is ensured, due recognition must be taken of the important rôle which bad eating habits have played in the development of the existing status. A reeducation of the patient's likes and dislikes is almost always indicated and is essential to the permanence of any weight gains which may be secured.

In addition to an adequate regime and the ability to follow the regime, a third requirement for success in the treatment of undernutrition is a genuine desire on the part of the patient to improve his condition and a capacity for self discipline. The reeducation of the habits of many years requires a certain strength of character even under the most favorable conditions. If a desire for a gain in weight is a whim of the moment or if the program is reluctantly accepted under pressure, a weight gain will be secured only insofar as, and only for as long as the patient persists. Significant changes in body weight cannot be produced in a few days. Success, therefore, depends upon the will of the patient to carry on.

METHODS OF OBSERVATION

The present study is based upon the observations made upon 41 patients during a period of four years. Twenty patients were studied on the metabolic pavilion of the hospital and 21 were office patients. Two patients of the hospital series were classed as failures in spite of known control. The data of these cases will be analyzed separately.

The weight records of private patients treated in the office were single observations of body weight without clothes which were taken on a good office scale at weekly or longer intervals. The weight records of the hospital patients were the average of three daily determinations taken under basal conditions on a special scale. In the estimation of probable true weight changes, it was felt that the averages of the weights observed on the day before, the day of, and the day after the beginning and end of a period of observation gave figures in which the influence of the normal daily fluctuation in residual water was minimized. In patients whose dietary treatment started on the first day, the average of only two days was taken. Likewise a few patients did not remain in the hospital beyond the period of observation and, therefore, lacked a weight record for the day following the cessation of treatment.

The food intake in the case of most of the office patients was not weighed. A few were required to purchase food scales and were provided with weighed diets. There was, therefore, no record of the exact intake of this group. All hospital patients were placed on a rigid metabolic regime. The observations of intake of this group were, therefore, of a high degree of accuracy.

OBSERVATIONS

Initial Status of Patients. Of the 39 patients successfully treated, there were 31 women and 8 men. This proportion, in our opinion, in no way in-

icates the relative predominance of undernutrition among women. The ages of the patients varied from 10 to 35 years in the hospital series and from 22 to 61 years in the office series. The average ages were 26 and 37 years respectively. It will be noted that with one exception, children were excluded from this study.

In stature the subjects varied quite as markedly as in age. In the hospital series, the height varied from 51.7 inches to 68 inches with an average of 63.5 inches. In the office series the variation was from 59 to 72.5 inches with an average of 65.5 inches.

The initial weights of the entire group averaged 46.9 kilograms. In the hospital series the weights varied from 21.2 kilograms to 54.1 kilograms with an average of 42.5 kilograms while in the office series they ranged from 35.4 kilograms to 63.1 kilograms with an average of 50.7 kilograms. For the purposes of this study, the relative weights are of greater significance than the absolute weights. The probable ideal weights of the individuals appear in column 5, tables 1 and 2. From the data in column 7, it will be seen that our subjects averaged 24 per cent below their ideal weights. In the hospital series they ranged from 13 per cent to 42 per cent with an average of 26 per cent while in the office series they averaged 22 per cent varying from 11 per cent to 39 per cent. Four patients, one in the hospital series and three in the office series, were not sufficiently below ideal weight to be classed as cases of undernutrition according to our defined standard. The hospital case, number 16, was a readmission for a second and postoperative period of metabolic study of patient number 15. This case will be discussed below. The three office patients presented clinical pictures similar to those of the rest of the series. They were included in order to emphasize the point that the degree of undernutrition does not necessarily influence the response to treatment. In the hospital series, patients 13 and 16 were repeat periods on patients 12 and 15 respectively. In each case the first period was preparatory to operation and the second period postoperative after a lapse of the several weeks immediately following the operation in order to permit metabolic stabilization. In the office series, patient Q was a repeat period three years after the first treatment (P) during which the patient dissipated much of her previous gain. T and V were also repeat periods on patient S at intervals of two and four years respectively. These repetitions will be discussed in more detail below.

The clinical pictures which were presented by these patients were greatly varied. In one patient, number 6 of the hospital series, the malnutrition might be described as *acute*. This patient was recovering from pneumonia followed by empyema. Patient 18 represented an acute exacerbation due to the rotoxicosis of a chronic malnutrition. Patient O of the office series had an acute malnutrition produced by a misguided diet. The remaining patients of both series could be classed as chronic types. In some the condition had existed since childhood. These cases fell into the so-called "hereditary" groups. The other patients had been underweight for many

years although in some cases a recent acceleration of the weight loss was responsible for consultation with the physician

The symptoms which were presented by our patients covered almost every system of the body. Palpitation, tachycardia, precordial pain, dyspnea, dizzy spells, especially on sudden changes of position or on prolonged exertion, were frequently mentioned. Many patients had discovered a limitation of their endurance. Some patients complained of irritability, nervous tension, inability to relax, insomnia. Others described weakness, lack of ambition and even lethargy as important symptoms. The majority of patients could be definitely regarded as unstable personalities.

The frequency of occurrence of specific endocrine disorders will vary with the conceptions of the observer as to what evidence indicates disorder of a given gland. In this series we have encountered frank thyrotoxicosis. Dysmenorrhea was frequent among women. Metrorrhagia and amenorrhea were noted, although in many other instances the menstruation was perfectly normal. Phenomena which are sometimes attributed to malfunction of the suprarenal glands such as instability of the circulatory apparatus, dizzy spells, low blood pressure, wide pupils, were often noted but were by no means constant. Headaches were frequent and often severe but no patient presented symptoms of intracranial pressure or other clear cut pituitary characteristics.

In many of our patients, especially of the hospital series, specific types of disease were found in association with the undernutrition. One patient was convalescent from acute rheumatic fever and showed evidence of an endocarditis which was apparently quiescent during the period of observation. Low grade pyelitis and cystitis were present in several of the women. Subacute or chronic pharyngitis was frequent. One patient suffered from chronic colitis. Another, a girl with a severe degree of undernutrition had ptosis of a kidney accompanied by severe pain but without infection. In general it might be said that these patients were very prone to low grade infections which could not be broken up. Although in several of the hospital patients, acute febrile states were present at the outset the records presented cover the afebrile and convalescent periods. The office patients were likewise frequently the subjects of persistent low grade infections, although in many cases these infections were not as severe as in the hospital group.

RESULTS OF TREATMENT

No data are available regarding the intakes of the office patients. Although a high caloric diet was calculated for many of them, the diet was only measured in most instances and, where the patient actually weighed the food, the figures are of only relative merit. Of the 18 hospital cases, complete dietary data are available for 16. The detailed analysis of these diets will be presented later⁶². It is of interest to note that the average caloric intake for the group was 3320 calories. With the exception of the absolutely low but relatively high figure 2310 calories in the case of the ten year

old patient, the lowest intake was 2790 calories. The highest average figure was 5090 calories. Thirteen of the 16 diets fell between 2800 and 3450 calories. This range of figures represents, therefore, the level of intake at which a significant rate of weight gain may be expected.

The weight changes which were observed have been arranged in tables 1 and 2. In the office group the increases varied from a minimum of 3.7 kilograms to a maximum of 14.3 kilograms. The average for this group was 8.2 kilograms. The hospital patients showed an average weight increase of 5.9 kilograms with a range from 1.7 kilograms to 17.7 kilograms. The average increase for the 39 patients was 7.1 kilograms. These figures are of considerably more interest when regarded from the point of view of body stature. Although at the outset the patients of the hospital group were 26 per cent below their ideal weights and those of the office group 22 per cent, after treatment the figures were 16 per cent and 9 per cent respectively. All but seven of the office group came well below the defined limit of undernutrition, whereas six of the hospital group were below this 15 per cent level. Again these data may be examined with reference to the change which was produced in the organism by the weight increase. After the dietary period, the hospital group patients had increased their bodies by 13 per cent of the initial mass and the office group patients by 17 per cent. Stated in other words, these patients increased their body mass by roughly one-seventh in these short periods. When expressed in relation to the time factor these figures acquire greater significance. It cannot be too frequently emphasized that the acquisition of a significant weight increase requires weeks and even months. In the office series the patients adhered to the program for from five to 16 weeks, on the average 10.9 weeks. In this average period of more than 2.5 months, they gained a total of 171.9 kilograms or on the average 8.2 kilograms per person. The rate of weight gain was, therefore, 78 kilograms per week. The 18 hospital patients gained a total of 106.2 kilograms or 5.9 kilograms per person. This was, however, accomplished in only five weeks (range two to 13.5 weeks) which gave a rate of change of 1.13 kilograms per week. Again, as above, these data may be restated to express the change which took place in the body. It was found that the office group changed their mass at the rate of 1.6 per cent per week while the hospital group averaged 2.8 per cent per week. Special attention may be directed to patient number 6 who increased his body at the rate of 7.1 per cent (or 1/14) per week for six weeks. This patient fell just short of a 50 per cent increase in body weight in a month and a half. Changes of body substance of these magnitudes of necessity require readjustments in body metabolism. The changes which were observed in certain aspects of metabolism will be described in subsequent papers.

The effects of treatment upon the symptomatology of the patients were striking. Practically all of the initial complaints entirely disappeared. The circulatory distress uniformly diminished and the irritability and nervous tension were appreciably improved. The thyrotoxic patient gained 9.1 kilo-

TABLE I
Office Series

1	2	3	4	5	6	7	8	9	10	11	12	13	14
Pt	Age Yrs	Sex	Height In	Ideal Wt Kilo	Initial Weight		Dura- tion Weeks	Final Weight		Weight Increase		Rate of Change	
					Kilo	Under Wt %		Kilo	Under Wt %	Kilo	%	Kg / /Wk	%/ /Wk
A	30	F	67	64.4	53.9	16	7	63.7	1	9.8	18	1.40	2.6
B	50	M	69½	75.3	57.6	24	12	67.1	11	9.5	16	.79	1.4
C	22	F	69½	65.8	55.4	16	13	67.2	+2	11.8	21	.91	1.6
D	25	F	65½	59.9	50.8	15	11	58.7	2	7.9	15	.72	1.4
E	51	F	65	67.1	48.1	28	12	58.5	13	10.4	21	.87	1.8
F	52	F	61½	61.7	40.1	35	10	47.5	23	7.4	18	.74	1.8
G	25	F	65	59.4	42.6	28	11	56.9	4	14.3	34	1.30	3.0
H	48	M	72½	83.9	63.1	25	9	70.5	16	7.4	12	.82	1.3
I	61	M	68	74.0	59.0	20	11	63.1	15	4.1	7	.37	.6
J	26	F	67	63.1	50.6	20	13	58.6	7	8.0	15	.61	1.2
K	42	F	67¾	68.5	60.3	12	12	69.1	+1	8.8	14	.73	1.2
L	52	F	67¾	72.6	54.9	24	8	61.5	15	6.6	12	.83	1.5
M	24	M	66½	64.4	56.2	13	7	59.9	7	3.7	7	.53	.9
N	28	F	64¾	59.9	50.0	16	15	56.5	6	6.5	13	.43	.8
O	33	F	64	60.3	41.7	31	5	46.3	23	4.6	11	.92	2.2
P	42	F	59	57.6	35.4	39	9	46.5	19	11.1	31	1.23	3.5
Q	45	F	59	58.1	39.2	33	16	48.1	17	8.9	23	.56	1.3
R	27	F	61¾	55.4	49.2	11	11	55.6	0	6.4	13	.58	1.2
S	32	F	66½	64.0	49.7	22	11	59.9	6	10.2	21	.93	1.9
T	34	F	66½	64.4	52.8	18	14	61.8	4	9.0	17	.64	1.2
U	36	F	66½	64.9	55.1	15	11	60.6	7	5.5	10	.55	1.0
Ave	37		65½	65.0	50.7	22	10.9	58.9	9	8.2	17	.78	1.6

TABLE II
Hospital Series

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Pt	Age Yrs	Sex	Height In	Ideal Weight Kilo	Initial Weight		Ave Caloric Intake Cal	Dura- tion Wks	Final Weight		Weight Increase		Rate of Change	
					Kilo	Under Wt %			Kg	Under Wt %	Kg	%	Kg / /Wk	%/ /Wk
1	32	Γ	64	59.8	41.9	30	2790	13½	53.3	11	11.4	27	.84	2.0
2	10	M	51¾	29.0	21.2	27	2310	3	22.9	21	1.7	8	.57	2.6
3	32	F	62½	56.7	38.9	31	2850	3	44.1	22	5.2	13	1.73	4.4
4	22	F	62	54.0	43.1	20	3200	4	47.5	12	4.4	10	1.10	2.5
5	28	M	66	64.4	49.5	23	2980	6	54.3	16	4.8	9	.80	1.6
6	35	M	68	71.3	41.4	42	5090	6	59.1	17	17.7	43	2.95	7.1
7	24	F	62	54.9	40.9	25	3280	12	52.9	3	12.0	29	1.00	2.4
8	20	F	62½	54.0	44.0	19	—	2	45.7	15	1.7	4	.85	1.9
9	31	F	64¾	60.8	47.6	20	3430	2	49.9	18	2.3	5	1.15	2.4
10	23	F	66½	59.9	44.6	26	3200	4	48.9	18	4.3	10	1.08	2.4
11	15	F	59	48.1	34.7	28	—	3	36.9	23	2.2	6	.71	2.0
12	33	F	63	58.5	35.1	40	3310	8	42.2	28	7.1	20	.89	2.5
13	33	Γ	63	58.5	39.5	32	3450	3	43.0	26	3.5	9	1.17	3.0
14	26	Γ	64½	58.1	49.4	15	3060	3	54.8	6	5.4	11	1.80	3.8
15	25	Γ	67	62.6	46.6	25	3260	5	52.8	16	6.2	14	1.24	2.7
16	25	Γ	67	62.6	54.1	13	3310	4	59.0	6	4.9	9	1.23	2.2
17	22	Γ	64½	57.2	46.7	18	2800	2½	49.0	14	2.3	5	.92	1.9
18	33	M	66½	66.7	46.4	30	4790	7	55.5	17	9.1	19	1.30	2.8
Ave	26		63½	57.6	42.5	26	3320	5	48.4	16	5.9	13	1.13	2.8

grams, and was relieved of many of his symptoms but his basal metabolic rate remained high and it was felt desirable to operate. The response of the patients with low grade infections was almost uniformly favorable. The frequency of colds diminished. Two cases of chronic colitis became free of symptoms.

It should not be assumed that a person who habitually has eaten 2000 calories per day or less can suddenly change to a 3000 calorie intake without a certain amount of physiological reaction. For the first few days practically all patients must literally force themselves to ingest the additional food. It should not be inferred that because a mechanical load was thrown on the gastrointestinal tract the digestion or absorption of food was defective. Quite the contrary was the case as will be shown later. A particular load appeared to be thrown upon the circulation not only to supply blood to the abdominal viscera but also to dissipate the extra heat which the meal produced. These and similar readjustments produced sensations which were often unpleasant. The sensations could be minimized by careful observation of the rest periods as described. This discomfort which the patients experience must be borne, though for only a few weeks, as the price which they must pay for the return to health.

It was mentioned above that two of the hospital patients failed to respond to treatment. One of these patients had dementia praecox. Although an adult of moderate frame this patient weighed only 75 pounds. No amount of pressure could induce the ingestion of even a maintenance diet. According to a subsequent report this patient died several months later, having a final weight of around 60 pounds. The second failure occurred in a young woman with probable multiple sclerosis who could not be induced to eat more than a maintenance diet. The failure of these patients to respond to dietary treatment resulted entirely from their inability to eat the prescribed diet.

Four of the patients described above have had repeated periods of observation. The two hospital patients 12 and 15 were treated for eight and five weeks respectively in preparation for necessary pelvic operations. Several weeks after their operations they were again placed on the high caloric regimes for periods of three and four weeks respectively. From the data listed in table 2, it may be seen that the rates of weight gain in both preoperative and postoperative periods differed in no essential detail. Of the office series, patient P followed the regime for nine weeks during which she gained 11.1 kilograms. Three years later she returned for treatment (Q) and in 16 weeks gained 8.9 kilograms. Patient S gained 10.2 kilograms after 11 weeks of treatment. Two years later (T) she gained 9.0 kilograms in 14 weeks and again two years later (U) she gained 5.5 kilograms in 11 weeks. Both of these women were mature and of considerable force of character. They were, however, unable to establish permanently new habits of eating. The prompt restoration of weight when the regime was reapplied indicates the absence of any unusual phenomenon. The progressive diminution in the weight gains of successive periods suggests the inability of these per-

sons to make the same inevitable sacrifices in the interests of weight gain a second and a third time although in both cases excellent records were attained on the first admissions

The permanence of the weight gains which have been secured is a matter of considerable interest. Only a few of the subjects of the hospital series could be followed for more than a year. Three of the patients (8, 10, and 11) are known to have lost their increases in weight. These three young women, who were quite typical of a large number of undernourished patients, were pampered persons who, yielding to family pressure, agreed to put on weight in the interests of health. These subjects gained as rapidly as the others during their periods of hospitalization. They followed the program outlined for only short periods after the two to four week stay in the hospital. Two other patients (15 and 18) have been followed for two and three years respectively. They followed the regime for more than nine and seven weeks during which they gained 11 and 9 kilograms respectively. After discharge they continued to follow instructions until they had far exceeded their ideal weights. They have maintained weights which are roughly 5 per cent greater than their ideal weights quite without effort for the periods noted. In the office series, only four patients have been lost from observation. Nine patients have maintained their weight changes for periods of one or more years. In the majority of these patients there has been a complete relief of the presenting symptoms. Five patients have failed to hold their new weight levels. In each case a return to the old habits of life could be held responsible. The records of patients P and S have been reviewed above. The histories of these patients emphasize the principle which we believe constitutes the basis for satisfactory treatment and permanence of weight gains. If a patient himself honestly wishes to improve his weight and if he has the strength of character to stand the distress and restrictions which are inevitable during the first few weeks of the regime, a permanent weight gain of any desired magnitude can be secured.

SUMMARY

1. Undernutrition may be regarded as the result of a food intake which is inadequate in comparison with the energy output. The evidence which has been advanced in support of specific etiologic factors, such as heredity, endocrine dyscrasias, and central nervous system disorders, fails to prove that the structural or functional abnormalities which have been observed are the cause of the undernutrition.

2. By the use of measures which produced an adequate positive energy balance, a series of patients representing various types of acute and chronic undernutrition has gained weight both in office and in hospital practice.

3. An adequate positive energy balance was secured not only by a high caloric intake but also by a reduction of energy output by a strict program of living.

4. As a result of the use of this method of treatment over a period of

four years, 21 office patients have averaged a weight increase of 8.2 kilograms in 10.9 weeks or 78 kilograms per week. Eighteen hospital patients have gained on the average of 5.9 kilograms in 5 weeks or 1.13 kilograms per week.

5 The correction of undernutrition in the patients described resulted in the disappearance of many diverse symptoms, an increased feeling of well-being and more especially an increased resistance to fatigue and to infection.

BIBLIOGRAPHY

- 1 APPEL, K. E., FARR, C. B., and MARSHALL, H. K. Insulin therapy in undernourished psychotic patients, preliminary report, *Jr Am Med Assoc*, 1928, xc, 1788-1789.
- 2 BENEDICT, F. G., MILES, W. R., ROTH, P., and SMITH, H. M. Human vitality and efficiency under prolonged restricted diet, *Carnegie Inst of Washington, Publication No 280*, 1919.
- 3 BERKMAN, J. M. Anorexia nervosa, anorexia, inanition and low basal metabolic rate, *Am Jr Med Sci*, 1930, clxxx, 411-424.
- 4 BLOTNER, H. Observations on the effect of insulin on thin persons, *Jr Am Med Assoc*, 1933, c, 88-92.
- 5 BUNN, W. H. Studies on undernourishment in industry, II, *Jr Indust Hyg*, 1923, v, 149-152.
- 6 CALDER, R. M. Anterior pituitary insufficiency (Simmonds' disease), *Bull Johns Hopkins Hosp*, 1932, l, 87-114.
- 7 CHAPIN, H. D. Do calories measure the value of food?, *Jr Am Med Assoc*, 1919, lxxviii, 1911-1912.
- 8 COLEMAN, W., and DuBOIS, E. F. The influence of the high-calorie diet on the respiratory exchanges in typhoid fever, *Arch Int Med*, 1914, xiv, 168-209.
- 9 DEUEL, H. J., JR., SANDIFORD, I., SANDIFORD, K., and BOOTHBY, W. M. Study of nitrogen minimum, effect of 63 days of protein-free diet on nitrogen partition products in urine and on heat production, *Jr Biol Chem*, 1928, lxxvi, 391-406.
- 10 DuBOIS, E. F. Basal metabolism in health and disease, 2nd Edition, 1927, Lea and Febiger, Philadelphia.
- 11 EDERER, S., and WALLERSTEIN, J. Die spezifisch-dynamische Wirkung und das vegetative Nervensystem, *Biochem Ztschr*, 1929, ccvi, 334-339.
- 12 Editorial. Dangers of fasting, *Jr Am Med Assoc*, 1929, xcii, 651.
- 13 FALTA, W., quoted by RICHTER⁵⁰.
- 14 GREGG, quoted by BURNETT, F. L. Progress of nutrition *New Eng Jr Med*, 1930, cciii, 118-128.
- 15 HOLT, L. E., and HOWLAND, J. Diseases of infancy and childhood, 1923, D Appleton and Co., New York, p 224.
- 16 HOUSSAY, B. A. The hypophysis and general metabolism, *Abstr, Jr Am Med Assoc.*, 1931, xcvi, 1639.
- 17 JACKSON, C. M. Structural changes when growth is suppressed by undernourishment. Mellon Lecture, 1932.
- 18 JONES, H. The influence of endocrine diseases on nutrition and basal metabolism, *Clin Med and Surg* 1928, xxvi, 476-484.
- 19 JOSEFSON, A. Zerebrale Magersucht, *Acta med Scandinav*, 1931, lxxv, 507-522.
- 20 KEETON, R. W., MACKENZIE, H., OLSON, S. and PICKENS, L. The influence of varying amounts of carbohydrate, fat, protein and water on the weight loss of hogs in undernutrition, *Am Jr Physiol*, 1931, xcvi, 473-490.
- 21 KLEITMAN, quoted by BURNETT, F. L. Progress of nutrition *New Eng Jr Med* 1930, cciii, 118-128.

- 22 KOEHLER, A E Differential diagnosis between hypothyroidism and hyposuprarenalism, Jr Am Med Assoc, 1928, xci, 1457-1462
- 23 KRAUSS, E Studien zur spezifisch-dynamischen Nahrungswirkung, Ruhe-Nuchternumsatz und spezifisch-dynamische Fleischerweisswirkung bei endogener Magerkeit, Ztschr f klin Med, 1930, cxii, 289-311
- 24 LABBÉ, M, and STÉVENIN, H Le métabolisme basal dans l'alimentation insuffisante, Presse méd, 1925, xxxiii, 401
- 25 LANGSTROTH, L Relation of American dietary to degenerative disease, Jr Am Med Assoc, 1929, xciii, 1607-1613
- 26 LEAKE, C, GRAB, J A, and SENN, M J Studies in exhaustion due to lack of sleep, symptomatology in rabbits, Am Jr Physiol, 1927, lxxxii, 127-130
- 27 LESCHKE, E Importance du système végétatif sur le métabolisme, Presse méd, 1931, xxxix, 1517-1519
- 28 LEVINE, V E Modern aspects of nutrition, pathology of malnutrition, Nebr State Med Jr, 1927, xii, 134, 175
- 29 LEVINE, V E Modern aspects of nutrition, pathology of malnutrition, Nebr State Med Jr, 1927, xii, 209
- 30 LUBLIN, A Lipogene und antilipogene Hormonwirkungen als Ursache endogener Fettsucht und Magersucht, Klin Wchnschr, 1929, viii, 2276-2278
- 31 LUBLIN, A Untersuchungen über die Kohlenhydratverwertung in nichtdiabetischen Organismus, das Verhalten des respiratorischen Stoffwechsels nach Kohlenhydratdarreichung unter dem Einfluss von Adrenalin und Substanzen mit adrenalinähnlicher Wirkung (Hypophen, Ephedrin, Ephetonin), Arch f exper Path u Pharmakol, 1927, cxxv, 229-241
- 32 LUSK, G The science of nutrition, 4th Edition, 1928, W B Saunders Co, Philadelphia
- 33 LUSK, G The physiological effect of undernutrition, Physiol Rev, 1921, i, 523-552
- 34 LUSK, G Specific dynamic action, Jr Nutrition, 1931, iii, 519-530
- 35 MACLEOD, J J R, MAGEE, H E, and MIDDLETON, W Insulin and increase in weight of young animals, Biochem Jr, 1930, xxiv, 615-618
- 36 MASON, E H, HILL, E, and CHARLTON, D Abnormal specific dynamic action of protein, glucose, and fat associated with undernutrition, Jr Clin Investigation, 1927, iv, 353-387
- 37 McLESTER, J S Nutrition and diet, 1927, W B Saunders Co, Philadelphia, p 419
- 38 METZ, R D Insulin in malnutrition, preliminary report, Jr Am Med Assoc, 1931, xcvi, 1456-1460
- 39 MILES, W R The sex expression of men living on a lowered nutritional level, Jr Nerv and Ment Dis, 1919, xlix, 208-224
- 40 MISSAL, M E, and JOHNSTON, M W The failure of pituitary substances to influence basal metabolism or specific dynamic response to food in a normal subject, Jr Lab and Clin Med 1929, xiv, 314-321
- 41 MITCHELL, H H The physiological effects of protein Jr Nutrition, 1929, i, 271-292
- 42 MITCHELL, H H, and CARMAN, G G Effect of excessive amounts of vitamin B on the basal metabolism of rats of different ages, Am Jr Physiol, 1926, lxxvi, 385-397
- 43 MITCHELL, H H, and CARMAN, G G The composition of the gains in weight and the utilization of food energy in growing rats, Am Jr Physiol 1926, lxxvi, 398-410
- 44 MOLLER, E Quantitative Verhältnisse des Stoffwechsels bei Unterernährung, illustriert durch 4 Fälle von nervöser Anorexie, Klin Wchnschr, 1924, iii, 1575-1579
- 45 MOTTRAM, V H Experiments in malnutrition Brit Med Jr, 1928, i, 88-91
- 46 PETERS, J P, WAKFMAN, A M, and EISENMAN, A J The plasma proteins in relation to blood hydration, the plasma proteins in malnutrition, Jr Clin Investigation, 1927, iii, 491-495
- 47 PETERS, J P, and VAN SLYKE, D D Quantitative clinical chemistry Vol I Interpretations, 1931, Williams and Wilkins Co, Baltimore, p 35

- 48 PETERS, J T Eine neue Formel zur Feststellung des Grades von Fettsucht oder Magerkeit, *Wien klin Wchnschr*, 1930, xliii, 70-71
- 49 RICHARDSON, H B The inadequacy of the measured diet as an index of the food metabolized, *Boston Med and Surg Jr*, 1923, clxxxix, 813-819
- 50 RICHTER, P F Klinische Vorlesungen über Stoffwechselkrankheiten, Magerkeit und Magersucht, *Deutsch med Wchnschr*, 1930, lvi, 339-340
- 51 RIECKER, H H, and CURTIS, A C Hypophyseal cachexia (Simmonds' disease) with report of 3 cases, *Jr Am Med Assoc*, 1932, xcix, 110-114
- 52 RUBNER, M, quoted by LUSK³³
- 53 RUBNER, M Über den niedrigsten Eiweissverbrauch, *Ztschr f d ges exper Med*, 1930, lxxii, 99-118
- 54 RUBNER, M Die Beziehung zwischen Nahrungsaufwand und körperlichen Leistungen des Menschen, *Naturwissenschaften*, 1927, xv, 203-212
- 55 SHELLING, D H Calcium and phosphorus studies, effect of calcium and phosphorus of diet on tetany, serum calcium and food intake of parathyroidectomized rats, *Jr Biol Chem*, 1932, xcvi, 195-214
- 56 SHERMAN, H C The chemistry of food and nutrition, 1928, The Macmillan Co, New York
- 57 SHORT, J J Increasing weight with insulin, preliminary report, *Jr Lab and Clin Med*, 1929, xiv, 330-335
- 58 SLONAKER, J R The effect of different per cents of protein in diet, intake and expenditure of energy, *Am Jr Physiol*, 1931, xcvi, 15-21
- 59 STEFKO, W Pathologie der Thymus- und Schilddrüse bei Inanition, *Krankheitsforschung*, 1931, ix, 70-80
- 60 STONE, W J Dietary facts, fads and fancies, *Jr Am Med Assoc*, 1930, xcv, 709-715
- 61 STRANG, J M, and McCLUGAGE, H B The specific dynamic action of food in abnormal states of nutrition, *Am Jr Med Sci*, 1931, clxxxii, 49-81
- 62 STRANG, J M, and COX, A B Analysis of high caloric diets in relation to weight changes (*ANNALS OF INTERNAL MEDICINE*, in press)
- 63 THANNHAUSER, quoted by RICHTER⁵⁰
- 64 THURMON, F M, and THOMPSON, W O Low basal metabolism without myxedema, *Arch Int Med*, 1930, xli, 879-897
- 65 YOUNG, J B Endemic edema *Jr Am Med Assoc*, 1932, xcix, 883-887
- 66 ZONDFK, H, and KOEHLER, G Über zerebral-hypophysäre Magersucht, *Deutsch med Wchnschr*, 1928, liv, 1955-1959

ULTRAHIGH FREQUENCY PYRETOTHERAPY OF NEUROSYPHILIS¹

A Preliminary Report

By WALTER M SIMPSON, M S , M D , F A C P ,

FRED K KISLIG, M D , F A C S ,†

and

EDWIN C SITTLER, B S (ENG),‡

Dayton, Ohio

IT IS NOW generally agreed that fever is essentially a protective and defensive mechanism. It is known that the fever which accompanies infection exerts an adverse influence upon the growth of bacteria, diminishes the potency of toxins, favors phagocytosis, and stimulates the development of immune bodies¹. The gradual abandonment of antipyretic drugs has naturally followed the recognition of these facts. More effective physical agents are now utilized to combat extreme hyperpyrexia.

The monumental researches of Wagner-Jauregg introduced artificially-induced fever as an important addition to the therapeutic armamentarium against many chronic afebrile diseases. The remarkable results which have been achieved with pyretotherapy in cases of general paresis, tabes dorsalis, diffuse central nervous system syphilis, and asymptomatic neurosyphilis leave no doubt as to the urgent need for the wider application of this form of treatment, particularly to the early stages of the disease with a view to preventing the late serious consequences. The purpose of the present investigation, now in its preliminary phase, is to determine whether or not fever therapy can forestall the disastrous late effects of syphilis §.

The fact that similar results have been obtained following the employment of a wide variety of fever-inducing agents (malaria, rat-bite fever, relapsing fever, typhoid vaccine and other foreign proteins, hot baths, hot air, electric blankets, diathermy, and radiothermy) indicates that the com-

* From the Diagnostic Laboratories, Venereal Clinic and Radiotherm Department of the Miami Valley Hospital and the Research Laboratory of the Frigidaire Corporation, Dayton, Ohio.

† This investigation was made possible by a grant from the Charles F. Kettering Foundation.

‡ Presented at the Seventeenth Annual Clinical Session of the American College of Physicians, Montreal, February 8, 1933.

§ Doctor Kislig died on February 7, 1933.

¶ With the cooperation of Charles F. Kettering, Sc.D., William Nesser, M.E., Thomas P. Sharkey, M.D., Worley Kendell, M.D., Arthur M. Culler, M.D., Eunice Fraizer, M.S., Carl McD. Ritter, B.S., Florence Storck, R.N., and Kathryn Rife, R.N.

§ This investigation had its inception in ideas expressed in a book by Paul de Kruif, Ph.D., entitled "Men Against Death," Harcourt, Brace and Co., N. Y., Chapt. 9, pp. 267-279.

mon denominator of all of these methods—fever production—is largely, if not entirely, responsible for the striking results which have been obtained

The ideal method for the artificial induction of fever is one which is subject to complete control by the physician and which can be employed with safety and comfort to the patient. Despite the brilliant results which have been obtained with therapeutic fever following inoculations with malaria, rat-bite fever, and relapsing fever, the fact remains that the engrafted infection is capable of producing great damage, even death, may be difficult to control, and is inconstant in its fever-producing properties. It is rarely possible to achieve adequately effective febrile reactions with foreign protein substances, hot baths, and hot air.

In September 1929, Neymann and Osborne,² and in March, 1930, King and Cocke,³ reported their experiences with artificial fever production with diathermy. Neymann and his collaborators⁴ have reported that the remission rate in paresis treated with diathermy exceeds the results obtained in a comparative series of clinically similar cases treated with malaria or rat-bite fever. The results obtained by King and Cocke in the treatment of an unselected group of paretics compared favorably with those reported for carefully selected paretics treated with malaria inoculations. More recently, many other observers (Perkins,⁵ Cortesi,⁶ Wilgus and Lurie,⁷ Prior,⁸ Bishop, Horton and Warren,⁹ Schamberg and Butterworth¹⁰) have found diathermy to be an effective method.

Since November 1931, we have been engaged in an investigation of the influence of an ultrahigh frequency field on neurosyphilis, gonococcal infections, arthritis, and vascular diseases of the extremities. The apparatus which we have employed for fever production was designed by Dr. Willis R. Whitney, director of the Research Laboratory of the General Electric Company. This apparatus has been adequately described by Whitney,¹¹ Carpenter and Page,¹² and DeWalt.¹³ Whitney had observed that workers exposed to the high frequency field produced by short-wave radio transmitters developed fever. The essential difference between a 1-kilowatt radio transmitter used for transoceanic broadcasting and the apparatus used for therapeutic fever production is that the energy is concentrated between two large condenser plates instead of being directed from an aerial. The name "radiotherm" has been applied to the altered radio transmitter. The heating effect is produced by a vacuum tube oscillator, composed of two 500-watt radiotrons, producing a high-frequency field of approximately 10,000,000 cycles per second (30 meter waves) between the condenser plates.

The radiotherm differs from the diatherm used for fever production in that it operates at a frequency approximately ten times as great, the diatherm operates at a frequency of approximately 1,000,000 cycles (300-meter waves). The spark gaps of diathermy produce damped waves while the vacuum tube oscillator of radiothermy produces an even flow of continuous waves. In fever production by diathermy, alternating currents of

high frequency pass between large electrodes applied directly to the skin surfaces of the anterior chest wall, abdomen and back. If the electrodes are not maintained in direct contact with the skin surface, arcing occurs, resulting in skin burns. In fever production by radiothermy, the patient merely lies on a stretcher between the condenser plates, no electrodes are applied to the skin surfaces.

Early in the course of this investigation it became apparent that the comfort of the patient would be greatly enhanced by utilizing some form of insulated air-conditioned cabinet. This measure was necessitated by the fact that short radio waves are concentrated in the drops of sweat which accumulate on the skin surface, producing arcing and burning. We found that the practice of wrapping the patient in many blankets, or using small hair-dryers in inadequately insulated cabinets, did not prevent arcing.

With the cooperation of Mr Charles F Kettering, director of the Research Laboratory of the General Motors Corporation, and the engineers of the Frigidaire Corporation, we have developed a highly efficient air-conditioned cabinet in which the nude patient lies, with his head extending outside the cabinet. The condenser plates are contained in the side walls of the cabinet. By passing a column of heated air (500-1000 cubic feet per minute at 150-200°F or 66-93°C, relative humidity, 0-10 per cent) over and under the patient, it is possible to dissipate sweat as it reaches the skin surface. The incorporation of recirculation ducts makes it possible to reutilize any quantity of the heated air. This refinement prevents arcing and adds enormously to the safety and comfort of the patient. The high temperature of the air is well tolerated because of its rapid movement and low relative humidity.

While the air-conditioned cabinet which we are now using appears to be eminently better than any other similar apparatus now available, we are not convinced that we have as yet perfected the method. We are now endeavoring to develop a much simpler and much less costly cabinet, with a view to further increasing the comfort of the patient. Furthermore, the high cost and the complexity of the vacuum tube oscillator, as now employed for fever production, and the relatively short life of the expensive radiotrons, have impressed us with the urgent need for the development of a cheap and simple fever-producing apparatus, which will eliminate the discomfort and hazards of the contact electrodes used in diathermy, and which will permit adequate air-conditioning and the employment of recording temperature devices.

Ordinarily it requires from 30 to 60 minutes to raise the rectal temperature from the normal level to the desired height (105-106°F or 40.5-41.1°C). The mouth and rectal temperatures, pulse and respiratory rates are recorded before the treatment is begun, and every 10 to 20 minutes during the course of the treatment. Because of the fact that there is no uniformity in individual response to fever production by high frequency methods, treatment must be strictly individualized. It is our practice to

proceed cautiously until we have determined each individual's reaction. During the first treatment, temperature readings are made every 5 or 10 minutes. Blood pressure determinations are made before the treatment, when the desired fever level is reached, at the end of the sustained febrile period, and when the temperature has reached the normal level. We have found the rectal temperature to be much more reliable than the mouth temperature. Since the available recording thermometers cannot be used in an electrostatic field of such intensity, mercury thermometers are employed. After the history, physical examination, and laboratory studies have determined eligibility for this form of therapy, the patient is asked to eat a light breakfast on the morning of each treatment. Several patients have been given amytal or paraldehyde by mouth 20 to 30 minutes before the treatment is commenced. If unusual restlessness and apprehension ensues, morphine is given by injection. Many patients, particularly after the first one or two treatments, require no sedatives.

We have observed the following contraindications in the employment of sustained artificial fever: advanced age, myocardial or renal insufficiency, active tuberculosis, aortic aneurysm, or rapidly progressive late neurosyphilis. The complexity of the various forms of high frequency apparatus in the present state of their development makes it imperative that their employment for therapeutic fever production should be restricted to hospitals, under the direct supervision of a physician who has thoroughly familiarized himself with the physical and technical principles involved. Furthermore, only adequately trained nurse-technicians should be entrusted with the responsibility of giving the treatments.

Until recently we have maintained the fever temperature produced by the radiotherm by covering the patient with heated blankets and transporting him rapidly to a warmed bed in an adjacent room. Here the patient was wrapped in two heated blankets, outside of which were placed eight "Hotpoint" flexible rubber electric pads. Four or five blankets were then placed outside the heater pads. With this procedure it is ordinarily possible to maintain the temperature at the desired level for the remainder of the five-hour period. The advantage of the constant heat production by rubber electric pads over hot water bottles is obvious. For several months we have also successfully maintained fever in insulated, moisture-proof electric blankets.

Even though the hazard of arcing is removed by this practice, many patients have complained of the heat in the secondary maintenance pack while they have voiced no objection to the heated air in the cabinet during the elevation of temperature with the radiotherm. The patient perspires freely in the pack, consequently the body is exposed to high relative humidity as well as to high temperature. To avoid this situation we are now permitting the patients to remain in the air-conditioned cabinet throughout the five-hour febrile period. The passage of the column of heated air, without the use of the radiotherm current, around the patient's nude body

is sufficient to maintain the temperature at the desired level. After the flow of high frequency current is stopped the rate of air flow is decreased and the vapor content of the air increased. Patients who have been subjected to both methods of temperature maintenance are grateful for the change to the cabinet-maintenance method. The temperature of the moving column of heated air is so much greater than the body temperature that there is no loss by radiation. The temperature of the column of air can be controlled readily to conform to the individual's tendency to attain a higher or lower temperature than that desired. If the patient's temperature should exceed the therapeutic limit of safety (106.8°F or 41.5°C) the temperature may be promptly lowered by reducing the air temperature of the cabinet.

Up to the present time we have completed the course of treatments of 100 patients. Each patient has received 10 treatments*. Each treatment has consisted of five hours of sustained fever, at weekly or biweekly intervals. With the exception of a few small first- and second-degree skin burns in those patients who were treated prior to the installation of the air-conditioned cabinet, no person has been injured during the 1000 treatments (5000 treatment hours).

While constant competent nursing attention is required throughout the entire treatment, the adoption of the air-conditioned cabinet for fever production and maintenance has greatly simplified this problem. One radio-therm machine, on wheels, can be used for the initial fever production of several patients by using several cabinets. By gradually lowering the temperature of the air in the cabinet after the febrile period is ended, the patient's temperature can be brought to approximately the normal level before he is removed from the cabinet.

We have learned that the sense of exhaustion commonly experienced by many of our patients early in the course of this investigation can be largely overcome by supplying large quantities of chloride-containing fluids. We discovered that most patients lost between three and five liters of sweat during the five-hour febrile period. The supplying of four to five liters of water during and immediately after each treatment satisfied the thirst, but did not favorably influence the symptoms of exhaustion, in fact, they appeared often to be augmented. A study of the blood chemical analyses revealed that while the creatinine, urea nitrogen, uric acid, sugar and calcium values showed the slight anticipated rise due to concentration of the blood and the increased metabolism of fever, the blood chloride values exhibited an average decline of 40 mg per cent at the end of the febrile period in approximately 80 per cent of the patients. In five instances the fall exceeded 100 mg, one of these patients developed typical hypochloremic tetany during the fifth hour of treatment. Some patients experienced nausea, vomiting, abdominal cramps, or muscular twitchings.

* Patients with gonococcal infections, arthritis or vascular diseases of the extremities usually require fewer treatments.

Chemical analysis of the sweat revealed an average sodium chloride content of 650 mg per cent. It became apparent that from 20 to 26 grams of sodium chloride were being withdrawn from the blood and tissues during each treatment. Gastric analyses, made at thirty-minute intervals during the febrile period, indicated that the free hydrochloric acid completely disappeared during the first 30 to 90 minutes. The combined acid exhibited a decided, but less complete, decline. A study of the urinary chlorides yielded less constant data.

These findings suggested the advisability of supplying chlorides during and immediately after each treatment. It was immediately apparent that the ingestion of four to six liters of 0.6 per cent sodium chloride solution largely abolished the sense of fatigue and exhaustion and practically eliminated nausea, vomiting, abdominal cramps and muscular twitchings. We have found the instillation of saline solutions per rectum to be much less effective.

The practice of replacing chlorides lost in the sweat has produced an apparently beneficial influence upon the blood chloride content, the majority now show no appreciable change in blood chloride values during or after the treatment. During the first few months of this investigation it was our practice to retain patients in the hospital for at least 24 hours following each treatment. Since the institution of the chloride-replacement regimen, eight months ago, it has not been necessary to keep patients in the hospital longer than one or two hours after the temperature has reached the normal level. This is particularly important in the management of early syphilis, where hospitalization would provide an insuperable obstacle to the general application of this form of treatment.

While we have obtained gratifying results in the treatment of gonococcal infections, certain forms of infectious arthritis, and vascular diseases of the extremities, we have largely centered our efforts on the application of this form of therapy to syphilis. Carpenter and Warren,¹⁴ Hinsie and his collaborators,¹⁵ and Tenney¹⁶ have employed radiotherm pyretotherapy in the treatment of various forms of neurosyphilis and have found that the percentage of complete remissions and improved cases compares most favorably with the results obtained with malaria therapy. Many observers (Kyrle,¹⁷ Matuschka and Rosner,¹⁸ Kauders,¹⁹ Paige, Rickloff and Osborne,²⁰ Neustaedter,²¹ Gugenheim,²² Reese,²³ Solomon and Epstein²⁴) have found malaria fever therapy plus specific chemotherapy to be much more effective than fever therapy alone. For this reason we have combined specific treatment (bismarsen, iodobismutol or tryparsamide) with the radiotherm treatments. Kyrle achieved remarkable results with both early and late syphilis by interposing the malaria-induced fever between two courses of salvarsan therapy. Kyrle concluded that therapeutic fever was much more effective when there was available a depot of salvarsan in the tissues. One great difficulty with the combination of malaria therapy with arsenicals is that the injection of the arsenic-containing drug usually inactivates the

malarial infection With high frequency fever it is possible to combine the two throughout the course of fever treatment This has been our practice We have continued the specific treatment (weekly injections) for at least four months following the last fever treatment Furthermore, if it should appear to be advisable to repeat the artificial fever treatment, the likelihood of successful fever production with a second or third inoculation with malaria is remote With high frequency fever therapy this handicap is entirely removed

Hinsie¹⁵ has subjected paretics to 70 hours (10 treatments of seven hours each) of radiotherm fever on the basis of the observation that 25 patients with general paresis obtained complete remissions after 70 hours of malaria-induced fever above 102°F (38.9°C) The conclusion of Wagner-Jauregg that eight malarial chills should be considered an optimum, rather than the 16 chills formerly employed, led us to reduce the number of hours of fever to 50 The fact that many of our patients appeared to experience the most marked improvement after the first six or seven treatments leads us to believe that 30 to 40 hours of fever might be equally beneficial in some individuals We intend to investigate further this possibility

Of the 100 patients who have received radiotherm treatments, 36 were treated for some form of neurosyphilis All of these patients were selected because of the failure of vigorous specific therapy to accomplish favorable results Twelve of these refractory patients satisfied the diagnostic requirements for general paresis, five were taboparetics, five were tabetics, four had diffuse central nervous system syphilis, six had asymptomatic neurosyphilis, and four had congenital syphilis involving the central nervous system

The scope of this communication permits only a summary of the results attained None of the paretics had the disease in a sufficiently advanced form to require commitment to a hospital for the insane Of the 12 early paretics all but one had a complete remission of all clinical symptoms at the conclusion of the combined radiotherm-specific therapy treatments, the other patient was considerably improved Marked improvement in the intellectual sphere was ordinarily observed after the first two or three treatments The psychic improvement was accompanied, with one exception, by decided gain in weight and strength The usual remark of the patients—"I feel like a new man"—was obviously justified by clinical observations Two patients with presumably well-marked optic atrophy experienced remarkable improvement in vision

The spinal fluid Wassermann and Kahn reactions were reversed to negative in three instances, became less positive in seven, and remained positive in two, at the end of the combined course of treatment In one the serologic reaction became negative during the next six months The delay in serologic response to malaria therapy in some successfully treated cases of paresis has been reported by many The cell count and albumin content of

the spinal fluid returned to the normal level in every instance. The colloidal gold curves became negative in three instances, in seven others they were appreciably lowered, in one instance there was no change, in one instance a first zone curve was elevated. The failure of the colloidal gold curve to exhibit constant relationship to clinical improvement is the usual observation following malaria therapy. Furthermore, the serologic findings do not parallel the degree of clinical improvement, particularly in late paresis. All but one of the paretics in this series are now engaged in their customary occupations.

In the five taboparetics, the most important observation has been the rapid improvement in mental orientation and the prompt subsidence of root pains. In four of the five cases, severe gastric crises or lancinating pains, or both, were the dominant feature of the disease, all were promptly relieved of the intense pain. One patient in this series had developed a recurrence of symptoms six months after malaria therapy (without specific therapy). The spinal fluid formulae showed essentially similar responses as in the paretic group. The pleocytosis and the increased organic solids were promptly reduced to normal levels. The Wassermann and Kahn reactions were reversed to negative in two instances, became less positive in two, and remained negative in another. No patient has experienced a recurrence of root pains during the period of observation (3 to 15 months).

In the tabetic group of five patients, ataxia (in all) and lancinating pains (in three) were the chief complaints. In one case in which periodic root pains had occurred for two years, and in which a typical tabetic gait had developed two months before the fever treatments were instituted, there occurred prompt disappearance of the lancinating pains (after the first treatment) and the tabetic gait (after the third treatment), neither has recurred since treatment was begun one year ago. In another case in which the tabetic gait had existed for approximately a year, considerable improvement in the ataxia was obtained, lancinating pains were promptly abolished in this case. In one case, with lancinating pains and a tabetic gait of two years' duration, no improvement in gait has occurred, but the patient is grateful for complete relief of the root pains. In two cases with ataxia of long duration (four and seven years), no improvement in gait was obtained, but both patients gained in strength and weight, in one the symptoms of "cord bladder" disappeared after the fourth treatment. The spinal fluid Wassermann and Kahn reactions were reversed to negative in one instance, became less positive in one, and remained negative in three.

In the group of patients with diffuse central nervous system syphilis were placed those who had various manifestations of symptomatic neurosyphilis, which could not be definitely classified as paresis, tabes, or taboparesis. The average age of the patients in this group was 30 years (13 years younger than the average age of the paretics, tabetics and taboparetics). All experienced neuro-recurrence following presumably adequate specific therapy. The average duration of syphilitic infection was seven

years, as contrasted with average duration of 15 years in the paretic, tabetic and taboparetic groups. All presented clinical and cytologic evidence of well-marked syphilitic meningitis. The cell counts and organic solids of all had reached the normal level at the conclusion of the fever treatments. The spinal fluid Wassermann and Kahn reactions became completely negative in three instances and less positive in two recently observed cases. The ocular complications of exudative uveitis in one case, multiple ocular palsies in another case, and active choroiditis in another patient, were arrested.

The response of the six patients with asymptomatic neurosyphilis was uniformly favorable. The only manifestation of neurosyphilis in this group was the presence of positive reactions of the spinal fluid. Even though asymptomatic neurosyphilis often occurs in early syphilis, none of our patients in this group has had the disease less than three years (average 4.5 years). In all five, the Wassermann and Kahn reactions of the spinal fluid were negative at the conclusion of the course of fever-specific therapy treatments. The cell counts and quantitative organic solids determinations were reduced to normal limits.

The response of many congenital syphilitics, with neuraxis involvement, to specific therapy is often practically nil. Our experience with four such cases provides hope for the future management of these refractory patients. The ages of these patients were 7, 12, 16 and 20 years. Two were classified as juvenile paretics on the basis of the spinal fluid formulae, while the other two were regarded as cases of diffuse central nervous system syphilis. Two patients were treated during active interstitial keratitis, all signs of keratitis disappeared without evidence of scarring after one five-hour fever in one case, the keratitis became more gradually inactivated after five treatments in the other case, with small residual opacities. The cell count and albumin content promptly declined to normal. The spinal fluid Wassermann and Kahn reactions were reversed to negative in one instance, became less positive in two, and remained negative in one. All are now in the remission stage as regards the clinical symptomatology.

While we are encouraged by the striking clinical and serologic improvement in this small series of patients, we realize that the time of these remissions is still too short to justify drawing any conclusions regarding their permanence. In view of the treacherousness of this infection, we intend to exert every effort to follow the progress of these patients throughout the balance of their lifetime.

A recent survey conducted by Clark²⁵ indicates that each year some 423,000 persons in the United States seek treatment for early syphilis. Since it has become more generally appreciated that examination of the spinal fluid as a routine measure is an indispensable part of the management of early, as well as late, syphilis, it has become apparent that at least one-third of persons with syphilis of less than two years' duration show some evidence of neurosyphilis. When changes characteristic of central nervous system invasion occur in the spinal fluid, the effect of treatment on the spinal fluid

formula becomes the first consideration in the subsequent management of the disease. Vigorous continuous specific therapy is often ineffective in arresting the progress of neurosyphilis. The remarkable results obtained by Kyrle,¹⁷ Wile and Davenport,²⁰ O'Leary,²¹ Gugenheim,²² Gougerot²³ and others in the treatment of asymptomatic neurosyphilis with malaria leaves no doubt of the challenging fact that the best time to treat paresis and tabes is before they develop to that stage. The results obtained in early neurosyphilis are eminently better than in the later stages of the disease.

More important than this observation, however, are the conclusions to be drawn from the brilliant results obtained by Kyrle in the treatment of syphilis during the first two years of its existence by the combined salvarsan-malaria-salvarsan regimen. The results were incomparably better than by any other method previously employed. Of 232 Wassermann-positive patients with early syphilis, the blood Wassermann reaction was favorably influenced in 230 (99.1 per cent) after a single combined course of treatment. Fifty-four of these patients exhibited Wassermann-positive reactions of the spinal fluid, all were reversed to negative and remained negative. When Matuschka and Rosner¹⁸ reported upon the work of Kyrle, after his untimely death, not one of these patients had developed a positive Wassermann reaction in either blood or spinal fluid during the five years covered by this classical report.

On the basis of these observations, it seems logical to conclude that the ideal time for the institution of combined specific therapy and fever therapy is immediately following the establishment of the diagnosis of syphilis. We have now undertaken the treatment of syphilis in the primary and secondary stages by the combined ultrahigh frequency fever-specific therapy method. These observations will be made the subject of a later report. The advent of methods for the controlled and safe production of artificial fever should stimulate vigorous inquiry in this field.

SUMMARY AND CONCLUSIONS

- 1 The age-old conception that fever is a destructive process has given way to the modern knowledge that fever is a protective and defensive mechanism.

- 2 The value of artificially-induced therapeutic fever is now firmly established. Fever production appears to be largely, if not entirely, responsible for the results attained with a wide variety of fever-inducing agents.

- 3 The need for a method of artificial fever induction which can be employed with safety and comfort to the patient, and which is subject to complete control by the adequately-trained physician, is apparent. The induction of fever with an ultrahigh frequency oscillator (short-wave radio transmitter), known as the radiotherm, in conjunction with an efficient air-conditioned cabinet, appears to fulfill these requirements.

- 4 The symptoms of exhaustion and fatigue, and the occurrence of nausea, vomiting, abdominal cramps, and muscular twitchings during the

sustained fever treatments are apparently largely due to the great loss of chlorides in the sweat. These symptoms are practically eliminated by supplying large quantities of chloride-containing fluids.

5 One hundred patients with syphilis, arthritis, gonococcal infections, or vascular diseases of the extremities have been subjected by us to 5000 hours of sustained fever therapy without evidence of injury, except for superficial skin burns in some of the patients treated before the development of the air-conditioned cabinet.

6 With due regard to the relatively short time during which our patients have been under observation, it may be stated that the results obtained with combined specific therapy and radiotherm pyretotherapy in cases of neurosyphilis are at least comparable to the results obtained with the more hazardous malaria-specific therapy regimen.

7 The fact that the most brilliant results are achieved in cases of early neurosyphilis, together with the remarkable observations of Kyrle in the treatment of early syphilis with the more hazardous, unreliable and time-consuming malaria-specific therapy regimen, make it probable that the logical time to institute combined fever and specific therapy is immediately following the establishment of the diagnosis of syphilis.

Note Because of the necessity of following the progress of patients subjected to this form of therapy for many years, we are restricting our investigations to patients who live in Dayton or in the immediate vicinity.

BIBLIOGRAPHY

- 1 REIMANN, H A. Significance of fever and blood protein changes in regard to defense against infection, *Ann Int Med*, 1932, vi, 362-374.
- 2 NEYMANN, C A, and OSBORNE, S L. Artificial fever produced by high frequency currents, preliminary report, *Ill Med Jr*, 1929, lvi, 199-203.
- 3 KING, J C, and COCKE, E W. Therapeutic fever produced by diathermy, with special reference to its application in the treatment of paresis, *South Med Jr*, 1930, xxiii, 222-228.
- 4 NEYMANN, C A, and OSBORNE, S L. Treatment of dementia paralytica with hyperpyrexia produced by diathermy, *Jr Am Med Assoc*, 1931, xcvi, 7-13,
NEYMANN, C A, and OSBORNE, S L. New method of producing fever—the treatment of general paresis, *Physiotherapy Rev*, 1931, xi, 47-50,
NEYMANN, C A, and KOENIG, M H. Treatment of dementia paralytica, comparative therapeutic results with malaria, rat-bite fever and diathermy, *Jr Am Med Assoc*, 1931, xcvi, 1858-1860.
- 5 PERKINS, C T. Diathermy treatment of dementia paralytica, a preliminary report, *Am Med*, 1931, xxvi, 546-552.
- 6 CORTESI, T. Therpirescia diatermica (metodo Neymann) nella cura della paralisi progressiva, *Ann di Neurol*, 1931, xlv, 1.
- 7 WILGUS, S D, and LURIE, L. Fever treatment of paresis by means of the diathermy current and electric blanket, *Ill Med Jr*, 1931, lx, 341-344.
- 8 PRIOR, G P V. Diathermy in the treatment of general paralysis of insane, *Med Jr Australia*, 1932, i, 882-888.
- 9 BICHOP, F W, HORTON, C B, and WARREN, S L. Clinical study of artificial hyperthermia induced by high frequency currents, *Am Jr Med Sci*, 1932, clxxxiv, 515-533.
- 10 SCHAMBERG, J F, and BUTTERWORTH, T. Diathermy in the treatment of general paralysis and in Wassermann-fast syphilis, *Am Jr Syph*, 1932, xvi, 519-534.

- 11 WHITNEY, W R Radiothermy, General Electric Rev , 1932, xxxv, 410-412
- 12 CARPENTER, C M, and PAGE, A B Production of fever in man by short radio waves, Science, 1930, lxxi, 450-452
- 13 DeWALT, K C A study of high frequency heating, Electronics, 1932, v, 338
- 14 CARPENTER, C M, and WARREN, S L Artificially induced fever in the treatment of disease, N Y State Jr Med , 1932, xxxii, 997-1001
- 15 HINSIE, L E, and CARPENTER, C M Radiothermic treatment of general paralysis, Psychiat Quart , 1931, v, 215-224,
HINSIE, L E, and BLALOCK, J R Treatment of general paralysis by radiothermy, Psychiat Quart , 1932, vi, 191-212
- 16 TENNEY, C F Artificial fever produced by the short wave radio and its therapeutic application, ANN INT MED , 1932, vi, 457-468
- 17 KIRLE, J Die Malariabehandlung der Syphilis, Wien klin Wchnschr , 1924, xxxvii, 1105-1109
- 18 MATUSCHKA, J, and ROSNER, R Die Malariatherapie der Syphilis, 1927, J Springer, Wien
- 19 KAUDERS, O Über die Nachbehandlungsperiode nach Malariabehandlung der progressiven Paralyse, Wien klin Wchnschr , 1931, xlv, 1199-1200
- 20 PAIGE, A, RICKLOFF, R J, and OSBORNE, E D Treatment of neurosyphilis, other than paresis, with malaria, N Y State Jr Med , 1931, xxxi, 1441-1446
- 21 NEUSTAEDTER, M The treatment of cerebrospinal syphilis with malaria, report of 26 cases, Jr Nerv and Mental Dis , 1931, lxxiii, 591-599
- 22 GUGENHEIM, F Das Schicksal der mit Malaria behandelten Luescerebrospinaliskranken, Ztschr f d ges Neurol u Psychiat , 1931, cxvxi, 525-541
- 23 REESE, H H Nonspecific and malarial therapy in neurosyphilis, Am Jr Syphilis, 1929, xiii, 348-359
- 24 SOLOMON, H C, and EPSTEIN, S H Tryparsamide in the treatment of neurosyphilis, N Y State Jr Med , 1931, xxxi, 1012-1015
- 25 CLARK, T Some public health aspects of syphilis, Venereal Disease Information, U S P H S , 1931, xii, 205-221
- 26 WILE, U J, and DAVENPORT, K M Malarial therapy of neurosyphilis other than uncomplicated dementia paralytica, Jr Am Med Assoc , 1931, xcvi, 1579-1585
- 27 O'LEARY, P A Treatment by malaria in asymptomatic neurosyphilis, Jr Am Med Assoc , 1931, xcvi, 1585-1586
- 28 GOUGEROT, H Malariatherapie préventive des syphilis nerveuses, Paris med , 1928, 1, 198-201

THE CLINICAL SIGNIFICANCE OF GASTRIC ACIDITY ¹

A Study of 6679 Cases with Digestive Symptoms

By ZACHARY SAGAL, M D, JEROME A MARKS, M D,
and JOHN L KANTOR, M D,
New York, N Y.

IN 1886, Jaworski and Gluzinski¹ introduced the generally accepted system of estimating gastric acidity in terms of "degrees" They then pointed out that the subject had been intensively studied for over a hundred years and apologized for adding another communication to the many already published Forty-six years later, Vanzant and her collaborators² called attention to the amazing fact that, despite the enormous amount of investigation, we have not even today any reliable standards of normal acidity for various ages Their explanation that this gap in our knowledge is due in part to the difficulty of getting a large number of normals for study seems rational All the previously reported studies of normals were made on comparatively small groups Bloomfield and Keefer³ studied 90 "normal" cases in one series and 30 in another Other studies (Bennett and Ryle,⁴ Apperly and Semmens,⁵ Dahl-Iversen,⁶ Moore et al,⁷ Henderson⁸ and others), were made on even smaller groups of young individuals, mostly college students The methods used by various investigators varied widely

The series reported from The Mayo Clinic comprises cases which were considered to be free from organic disease of the gastrointestinal tract, but they were not free from digestive disturbances It is true that if we consider a person's digestion as normal only when he can eat with impunity anything within reason, in any quantity and at any time, very few people, especially those past middle age, could qualify as normal The difficulties in studying normal acidity in the human are therefore manifold Not only is it "not easy to get several thousand normal persons to submit to gastric intubation" (Vanzant et al), but it is doubtful whether any appreciable number of strictly normal persons could be found, particularly in the higher age groups, unless absence of gross pathology is accepted as the criterion of normality

In discussing Vanzant's paper before the American Gastro-Enterological Association, in May 1931, one of us (J L K) pointed out that our figures on gastric acidity collected from office and clinic patients, all of whom complained of gastrointestinal symptoms, corresponded to those of the

¹ Read before the American Gastro-Enterological Assoc at Atlantic City, N J, May 2, 1932

Mayo group, collected presumably from normals. In perusing their paper, however, we find that our material resembles theirs more closely than was at first supposed. The cases of organic disease, which Vanzant excluded from her studies, constitute a large proportion in a hospital of the type of The Mayo Clinic, but are in a small minority in a gastrointestinal clinic for ambulatory patients or in the office of a gastroenterologist.

Inasmuch as it is practically impossible to secure perfectly normal individuals in the various age groups, the next best thing is to make a statistical study of large numbers. This communication is based on the study of a series of cases which we have been accumulating for the past twelve years. Our material lends itself to special grouping according to social status and partly to occupation, as well as to age and sex. We have also had the opportunity of following the gastric acidity in several individuals over a period of years, with results which, as far as we know, have not been reported in the literature.

MATERIAL

Of the 6679 test meals used as a basis for this communication, 2401 were performed at the Vanderbilt Clinic, 1062 in a clinic maintained by a labor organization of the needle trades, and the remaining 3216 on private patients in our respective offices. All the titrations at the Vanderbilt Clinic were carried out by the same technician, while the other tests were performed either by us or under our direct supervision.

METHODS

All the patients received a Boas-Ewald test meal, slightly modified, namely four Uneeda biscuits and two glasses of water, the change from bread to crackers insuring more uniformity and greater convenience. A single extraction was made at the end of 45 minutes. For the titrations of free HCl and total acidity, Toepfer's reagent and phenolphthalein were respectively employed as indicators.

In classifying our cases in reference to acidity, we divided them into four major groups. Those showing no free HCl were classed as achlorhydria. Those showing free HCl under 20 degrees or total acidity under 40 were diagnosed subacidity. Those showing free HCl above 40 or total acidity above 60 were grouped as hyperacid. Thus, only those which had free HCl between 20 and 40 and total acidity between 40 and 60 were considered as "normal." A fifth group comprising a small number of cases, showing free HCl below 20 and total acidity above 60, we termed "dissociated acidity" and did not include in our basic tables.

We studied separately the data obtained in the clinic clientele from that of the office patients in an effort to detect any difference based on social and economic status. We also segregated for separate study a group of patients employed in the tailoring industry, almost all of them belonging to the Jewish race.

Inasmuch as the material studied is composed entirely of ambulatory cases as they appear in the gastrointestinal clinics and in offices of gastroenterologists and the proportion of patients with organic disease is comparatively small, the latter were included in our series. However, in order to determine the possibility of appreciable error, all cases of carcinoma, peptic ulcer and gall-bladder disease were excluded in a part of our material. The resulting percentage distribution and curves are practically the same as before the exclusions (Tables 1 and 2)

TABLE I
Age and Sex Factors in Gastric Acidity (2286 Cases)

Ages	Percentages							
	Males—1402				Females—884			
	<i>A</i>	<i>S</i>	<i>N</i>	<i>H</i>	<i>A</i>	<i>S</i>	<i>N</i>	<i>H</i>
11-20	2	20	26	50	0	22	48	30
21-30	2	15	36	46	3	25	46	24
31-40	2	9	33	55	7	27	36	29
41-50	3	8	26	61	13	22	42	22
51-60	5	20	24	50	15	21	34	29
61-70	20	8	20	52	20	16	20	44

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity

TABLE II
Age and Sex Factors in Gastric Acidity after Organic Pathology Was Excluded

Ages	Percentages							
	Males—1173				Females—766			
	<i>A</i>	<i>S</i>	<i>N</i>	<i>H</i>	<i>A</i>	<i>S</i>	<i>N</i>	<i>H</i>
11-20	3	23	27	46	0	23	50	28
21-30	3	16	40	41	4	25	46	25
31-40	3	10	37	50	8	25	37	30
41-50	5	10	27	58	14	22	23	41
51-60	6	23	26	45	12	20	40	28
61-70	25	10	25	40	15	0	38	46

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity

Wherever we encountered groups of less than 25, we did not consider them in plotting our graphs, as percentage calculations on small numbers are extremely unreliable and often incorrect. It is for this reason that figures below the age of ten are not included in our paper.

FINDINGS

The greatest relative number of patients at all ages up to 70 have high acid figures (Figure 1 and Table 3). Next in order are the moderate acidities (so-called normals), then the low and finally the achlorhydrias. The greatest percentage of high acidities is found in the fourth and fifth decades, gradually declining thereafter. The proportion of patients with

TABLE III
Gastric Acidity and Age (6679 Cases)

Decade	Cases	Per cent			
		<i>A</i>	<i>S</i>	<i>N</i>	<i>H</i>
11-20	216	2	23	32	43
21-30	1744	4	23	37	36
31-40	3141	5	19	32	44
41-50	1461	10	20	24	46
51-60	796	16	20	25	38
61-70	277	22	18	25	35
71-80	44	18	40	16	26

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity

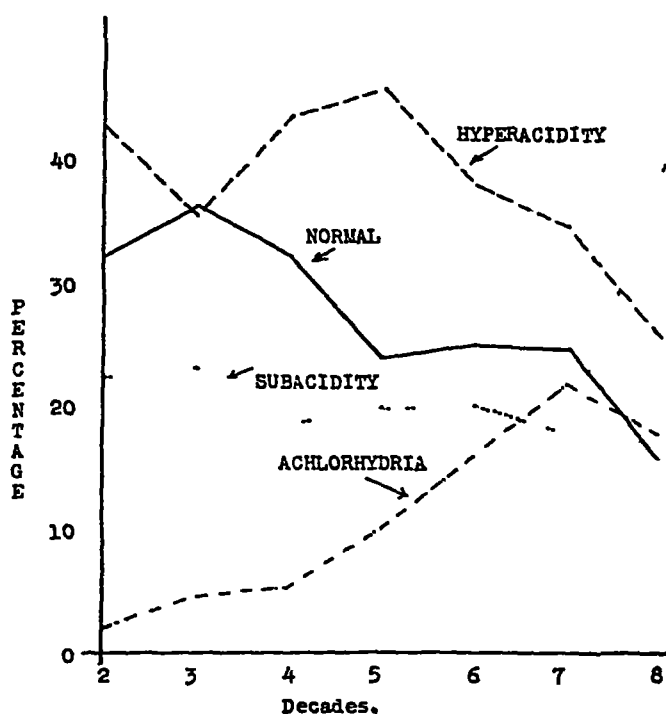


FIG 1 Gastric acidity in relation to age (6679 cases)

what we are accustomed to consider normal acid figures slowly decreases from the third decade on. The low acidities fluctuate but little until the last decade when they show a definite rise. There is a progressive increase in the incidence of achlorhydria up to the age of 70, with slight diminution beyond that point. However, the number of cases in our series above that age is too small for positive statistical statements.

One group of patients, almost exclusively of the Jewish race and belonging to a labor union of the tailoring trades, showed a very high incidence of hyperacidities for all decades. As in the other groups studied, the peak was reached in the fifth decade, the entire curve being on a higher level. The other acidity curves were practically the same as in the other groups (Table 4).

TABLE IV
Gastric Acidity and Age, Needle Trades Group (1062 Cases)

Decade	Cases	Per cent			
		<i>A</i>	<i>S</i>	<i>N</i>	<i>H</i>
11-20	29	0	24	45	31
21-30	358	3	25	28	34
31-40	416	3	13	34	50
41-50	205	5	13	24	58
51-60	49	8	28	18	46
61-70	4	50	0	0	50

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity

In a group of relatively wealthy private patients, the incidence and peak of high acidities were distinctly lower than in the working class group (Table 5)

TABLE V
Gastric Acidity and Age, Private Patient Group (2000 Cases)

Decade	Cases	Percent			
		<i>A</i>	<i>S</i>	<i>N</i>	<i>H</i>
11-20	65	2	31	29	38
21-30	500	5	32	32	31
31-40	595	5	28	31	36
41-50	417	13	27	22	38
51-60	277	17	25	25	32
61-70	114	25	25	23	27
71-80	24	12	54	8	25

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity.

The figures obtained on the Vanderbilt Clinic patients, presumably belonging to the poorer classes, of all races and creeds, showed acidities and curves between the extremes just described (Table 6)

TABLE VI
Gastric Acidity and Age, Vanderbilt Clinic Cases (2401 Cases)

Decade	Cases	Per cent			
		<i>A</i>	<i>S</i>	<i>N</i>	<i>H</i>
11-20	66	3	16	32	49
21-30	551	6	19	34	41
31-40	712	7	16	31	46
41-50	617	11	19	25	45
51-60	333	19	16	24	41
61-70	111	20	15	30	35
71-80	11	18	27	27	27

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity

The generally recognized very high incidence of hyperchlorhydria in duodenal ulcer, and achylia or marked hypoacidity in gastric carcinoma is shown in table 7. The distribution in gall-bladder disease is the same as

TABLE VII
Gastric Acidity in Certain Diseases

	No of Cases	Percentages			
		<i>A</i>	<i>S</i>	<i>N</i>	<i>H</i>
Gastric Carcinoma	41	45	40	10	5
Duodenal Ulcer	357	0	3	15	82
Gastric Ulcer	46	2	23	26	49
Gall-bladder Disease	247	9	28	32	31

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity

that ordinarily found in the corresponding age periods

The acidity means were calculated for each decade (Figure 2) The free and total acidities maintain a fairly constant level through the fifth decade when they show a gradual drop

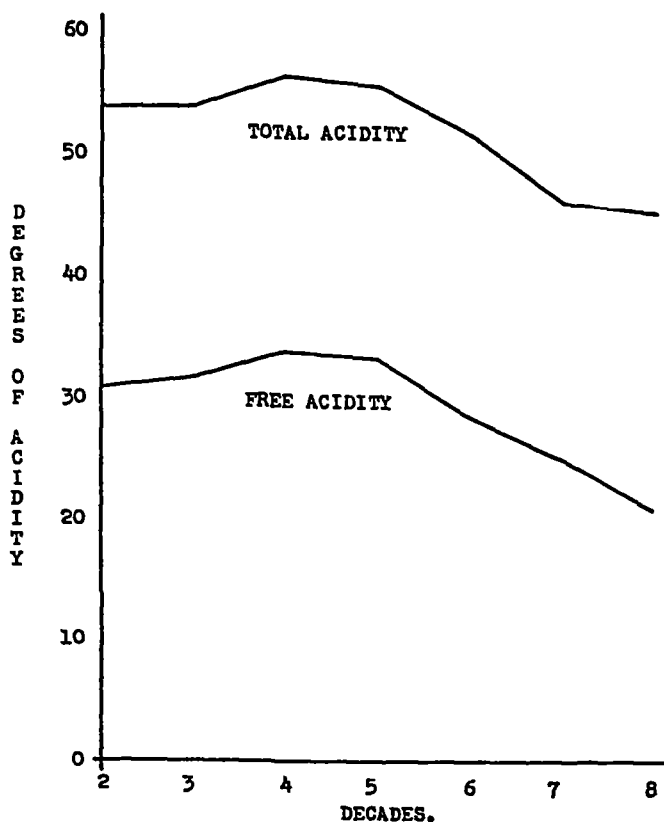


FIG 2 Mean gastric acidity by decades (6679 cases)

As regards sex, we found, as did other investigators, that acidity in females runs generally lower than that in males. The difference corresponds to almost ten degrees in both the free and the total ranges (Figure 3)

In one series of 2000 cases, the dissociated acidity group was studied. Twenty-two cases were found, making an incidence of about 1 per cent

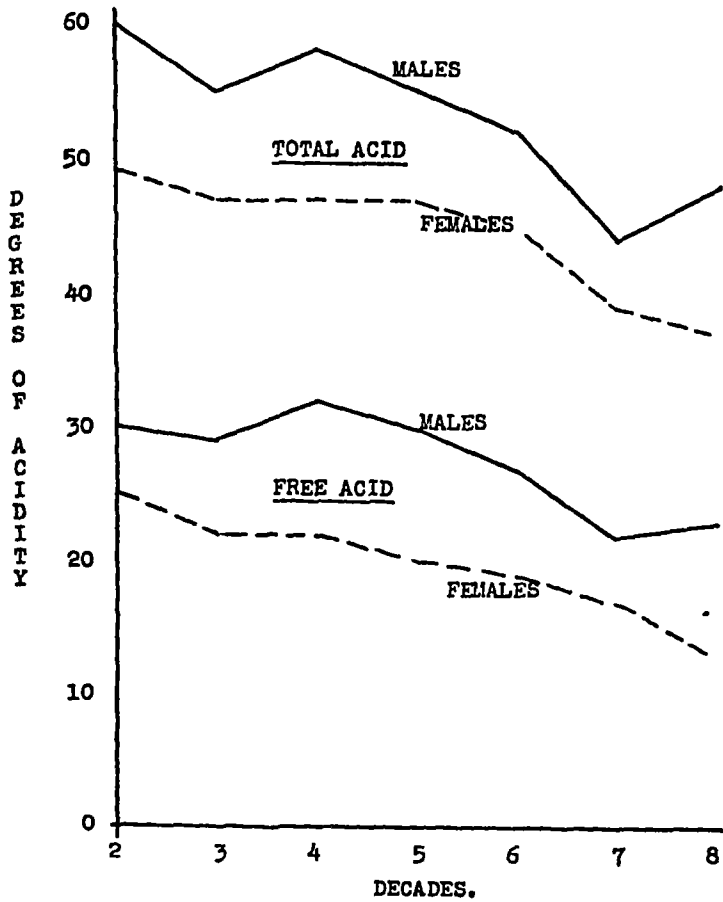


FIG 3 Gastric acidity means in relation to age and sex

TABLE VIII

Case 1					Case 2				
G I Neurosis—Fem					G I Neurosis—Fem				
Date	Age	Free HCl	Total Acid	Class	Date	Age	Free HCl	Total Acid	Class
July 1922	42	8	16	S	June 1924	48	14	28	S
July 1923	43	0	15	A	Sept 1931	55	0	4	A
Dec 1928	48	0	19	A	Apr 1932	56	0	5	A

Case 3					Case 4				
Duodenal Ulcer—Male					G I Neurosis—Male				
Date	Age	Free HCl	Total Acid	Class	Date	Age	Free HCl	Total Acid	Class
Oct 1920	33	41	88	II	June 1925	78	11	33	S
Apr 1927	40	30	68	II	May 1925	78	11	38	S
June 1930	43	32	66	II	June 1929	82	2	15	S
Apr 1932	45	18	58	S	Dec 1930	83	2	19	S
					Nov 1931	84	0	7	A

A stands for achlorhydria, S for subacidity, N for normal, II for hyperacidity

The only remarkable feature noted was that ten cases in the group, or 45 per cent, suffered from gall-bladder disease

The results of repeated test meals on the same individuals show several interesting features. In the first place a surprising constancy in the successive sets of figures is regularly obtained when the tests are performed under standardized conditions within relatively short periods of time, particularly in younger individuals. If the period of observation is prolonged to five years or more, especially after a decade, there appears a definite tendency, more so in older patients, to show a diminution or loss in acidity (Table 8). Thus, high figures become lower and low figures drop into the achlorhydria class. Exceptions, of course, do occur, as illustrated in the case of heterochylia in a neurotic individual, who, in the course of four and one-half years, had five analyses and managed to be in every class once and in the normal class twice (Table 9).

TABLE IX
G I Neurosis—Male

Date	Age	Free HCl	Total Acid	Class
1 Dec 9, 1926	52	6	31	<i>S</i>
2 Dec 9, 1927	53	38	58	<i>N</i>
3 Dec 19, 1930	56	0	13	<i>A</i>
4 Feb 28, 1931	57	32	61	<i>H</i>
5 Apr 11, 1931	57	38	59	<i>N</i>

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity

DISCUSSION

What Constitutes Normal Acidity It is quite evident that we cannot accept one standard for all age periods. Some authors, especially those who have departed from the Boas test meal, digress from the usual normals of 20 to 40 degrees for free HCl and 40 to 60 for total acidity and name their own figures. Thus, Lerman,⁹ using the alcohol and histamine test meal, considers the normal acidity range to be 20 to 70 degrees for free HCl. Bloomfield suggests that we dispense with the term normal and classify the cases as high, medium, low, and anacid.

The fact that some individuals are always achlorhydric and that the absence of free HCl was found in children (Wright,¹⁰ Hertz,¹¹ Jacobsen,¹² and even in the newborn, Hess¹³) justifies the inference that lack of acid is a constitutional characteristic with some individuals and is "normal" for that particular type. Carlson¹⁴ has long maintained that all grades of acidity as well as anacidity are found in a considerable number of "normal" individuals. Furthermore, it has been observed that a given type of gastric secretion is characteristic of certain families, high acidities being common in some and low acid figures or even achlorhydria in others (Dauwe,¹⁵ Martinez,¹⁶ Apperly and Norris¹⁷). In short, normality is generally a very elastic term. In the present state of our knowledge, it is evident that age

and sex must be considered in any discussion of normal standards Utilizing the acidity means already referred to, it is an easy matter to construct a simple table, similar to that of height and weight or blood pressure, that might serve as a guide to the clinician in every-day practice An arbitrary deviation of ten degrees on either side of the means would give the results in round figures, as shown in table 10 All cases falling within the above

TABLE X
Average Range of Acidity Distributed According to Age and Sex

	Free HCl		Total Acidity	
	Male	Female	Male	Female
11-20	20-40	15-35	50-70	40-60
21-30	20-40	15-35	45-65	35-55
31-40	20-40	15-35	45-65	35-55
41-50	20-40	10-30	45-65	35-55
51-60	15-35	10-30	40-60	35-55
61-70	10-30	10-30	35-55	30-50
71-80	10-30	5-25	35-55	30-50

A stands for achlorhydria, *S* for subacidity, *N* for normal, *H* for hyperacidity

limits could, therefore, be designated as moderate acidities (discarding the term normal), while others would be considered as high or low, as the case might be

This table represents a rough scale somewhat more accurate than the old fixed forms in which age and sex were not considered, but without any pretense to such statistical accuracy as is manifest in the painstaking work of Vanzant and her collaborators

Diagnostic Value of Gastric Acidity Determination Inasmuch as all grades of acidity are found in healthy individuals, it follows that the diagnostic significance of acidity tests is only of secondary importance—it has only a confirmatory value Thus, in the presence of achlorhydria, the evidence in favor of duodenal ulcer must be overwhelming to make the diagnosis Likewise, a diagnosis of primary anemia would hardly be in keeping with high or moderate acid figures At this point we wish to call attention to our observation that dissociated acidities (low free HCl and high total acidity) are suggestive of gall-bladder disease The reason for the dissociation probably lies in the greater amount of duodenal regurgitation and higher combined acidity

The Significance of Achlorhydria The subject of achlorhydria has been discussed in great detail by numerous writers Ehrman,¹⁸ who introduced the conception of simple achylia, Martius,¹⁹ Faber²⁰ and lately Bloomfield and his collaborators, as well as many others, have studied it from many angles It is of particular interest as a possible predisposing factor to serious organic disease, such as gastric carcinoma and pernicious anemia As precursors of carcinoma of the stomach, Hurst²¹ puts achylia and gastritis in the first place He cites two cases which were achlorhydric long before the

cancer developed We have also had two cases which had no free HCl with negative roentgenological findings for six and eight years before they developed cancer of the stomach Unfortunately, it is very rarely that patients with carcinoma of the stomach have records of previous test meals The achlorhydria clinic which Bloomfield has inaugurated is therefore a step in the right direction and is worth emulating

The Significance of Low and High Acidities The increasing incidence of achlorhydria with advancing age suggests the probability that gastric acidity gradually fails with advancing years The number of achlorhydrics is augmented by new recruits from among those with low acidities The low acidity group is in turn replenished from the higher acidity groups Some evidence of this was presented above The process of decline does not seem to begin until the fifth decade is passed In all of our groups, the greatest percentage of high acidities is found in the fifth decade One may infer that probably our mode of living and dietary habits tend to stimulate gastric function, producing a greater proportion of high acidities up to that point After the fifth decade, however, when all bodily functions are in the decline, gastric secretion also begins to diminish The fifth decade thus constitutes a turning point and diminishing gastric acidity may be regarded as one of the indications of approaching old age such as loss of hair and teeth, diminishing activity of internal secretions, arteriosclerosis, and so on

On the other hand, high gastric acidity persisting into old age may be considered as an indicator of longevity Only the hardier individuals reach the eighth and ninth decade and they seem to be the ones who have high gastric acidity It is interesting to observe the contradictory reports as regards acidity in old age Dedichen²² and Davies and James²³ reported low acid figures, while Rafsky²⁴ found hyperacidity to be the rule in a group of exceedingly old individuals (70 to 90 years of age)

Practical Value of Test Meals It is not within the province of this communication to enter into a discussion of the relative value of the many different test meals that were suggested in the past or are still in use While the data reported here are based on results obtained with the single aspiration after a Boas-Ewald test meal, we do not wish to be misunderstood as advocating this method in preference to or to the exclusion of all others For thorough discussion of the merits and drawbacks of the various procedures, the reader is referred to the writings by Boas,²⁵ Isaak-Krieger,²⁶ Andresen,²⁷ Garbat,²⁸ Gaither,²⁹ Smithies,³⁰ and others Our feeling is that for practical purposes, it matters little what is used for a test meal or how many extractions are made We would not even object to the use of fresh cabbage juice, as suggested by Orlowsky,³¹ if one does not mind the trouble of procuring it in all seasons Any test meal with a single aspiration will serve to classify the patient as to the type he belongs to, whether he secretes gastric juice of the high or low titre It is only the exceptional case that will give low figures with one method and high ones with another

It is now fairly generally accepted that with regard to gastric acidity

there are several types, differing constitutionally in the same manner as the sthenic and the asthenic, or the hypersensitive and the hyposensitive. From the standpoint of predisposition to various diseases it is very important to determine to which group the patient belongs and to classify him accordingly.

It is of importance to find out the low acidities as well as the anacidities, as it seems quite possible that the hypochlorhydrias are potential achlorhydrias and that the increase in achlorhydrias in the later decades is due to this factor. The importance of doing a test of the gastric secretory function on every patient cannot be overemphasized. One might go even further and say that it should be included in every periodic physical examination.

Any symptoms even remotely suggesting an early peptic ulcer should be considered seriously in the hyperchlorhydric and the patient kept under observation. On the other hand, it is known that pernicious anemia is preceded by achlorhydria long before any other suspicious evidence makes its appearance. Our knowledge of the achlorhydria preceding the development of gastric carcinoma is so far very limited and further investigation of this relationship is desirable.

It is also essential to know for dietetic considerations, the kind of gastric juice the individual secretes. Subjects with a tendency to hyperacidity should avoid spicy and other foods which stimulate gastric secretion. On the other hand, low acidity calls for an entirely different diet. One cannot tell, except empirically, what foodstuffs are most suitable for any particular individual unless some sort of test is done. Many cases of heartburn have moderate or low gastric acidities, even achlorhydria, and the medicinal treatment is to be guided accordingly.

SUMMARY

- 1 A series of 6679 test meals is analyzed according to age and other factors.

- 2 Age, next to constitutional predisposition, appears to be the dominating factor in gastric acidity. Thus the greatest incidence of high acidity occurs in the earlier age groups, while the low acid figures predominate in the later decades.

- 3 It is well known that certain diseases are associated with special ranges of acidity (e.g. duodenal ulcer with hyperacidity, pernicious anemia and cancer of the stomach with achlorhydria), but there is evidence to indicate that these acid levels precede the development of the disease, just as they persist after its cure.

- 4 It would appear that the degree of acidity—a constitutional factor—predisposes to a given disease, rather than that the disease produces a change in acidity.

- 5 It appears that the fifth decade constitutes the peak of functional activity as evidenced by the greater proportion of high acidities, while diminishing gastric acidities may be considered as evidence of aging, analogous to presbyopia, hypertension, arteriosclerosis, and the menopause.

6 The presence of high acid values in old age may be considered as an index to longevity

7 The determination of gastric acidity is of practical value as an index of predisposition to certain diseases and as a guide to important therapeutic procedures (diet, medication)

8 Evidence is presented that in older patients, under observation for comparatively long periods, there is a tendency to a diminution or loss of gastric acidity

9 A table of average values of gastric acidity, arranged according to age and sex, is proposed instead of the more arbitrary standards now in use

We wish to express our appreciation of the collaboration of Dr Harry Gauss, now of Denver, Colo., in preparing some of the earlier statistical material for this paper

BIBLIOGRAPHY

- 1 JAWORSKI, W, and GLUZINSKI, A Experimentell-klinische Untersuchungen über den Chemismus und Mechanismus der Verdauungsfunktion des menschlichen Magens im physiologischen und pathologischen zustande, nebst einer Methode zur klinischen Prüfung der Magenfunction für diagnostische und therapeutische Zwecke, *Ztschr f klin Med*, 1886, xi, 50-98, 270-293
- 2 VANZANT, F R, ALVAREZ, W C EUSTERMAN, G B, DUNN, H L, and BERKSON, J The normal range of gastric acidity from youth to old age an analysis of 3746 records, *Arch Int Med*, 1932, xlix, 345-359
- 3 BLOOMFIELD, A L, and KEEFER, C S Gastric acidity relation to various factors such as age and physical fitness, *Jr Clin Investigation*, 1928, v, 285-294—Rate of gastric secretion in man, *Jr Clin Investigation*, 1927, iv, 485-494—Clinical physiology of the stomach, simultaneous quantitative observations on gastric secretory volume, acidity and motility, *Arch Int Med*, 1926, xxviii, 145-158
- 4 BENNETT, and RILE Studies in gastric secretion V A study of normal gastric function based on the investigation of one hundred healthy men by means of the fractional method of gastric analysis, *Guv's Hosp Rep*, 1921, lxvi, 286-318
- 5 APPERLY, F L, and SEMMENS, K Fractional test-meal in normal students, comparison of results with those of other observers, *Med Jr Australia*, 1928, ii, 237-239
- 6 DAHL-IVERSEN, E Examens de la sécrétion gastrique chez des hommes normaux, *Lyon Chirurg*, 1926, xxiii, 14-29
- 7 MOORE, B, ALEXANDER, W, KELLY, R E, and ROAF, H E On the absence or marked diminution of free HCl in gastric contents, in malignant disease of organs other than stomach, *Proc Roy Soc, London*, 1905, lxxvi, 138-159 (*Abstr Lancet*, 1905, i, 1120-1124)
- 8 HENDERSON, M G Investigation of the gastric contents of 100 persons by means of the fractional test meal, *Practitioner*, 1929, cxliii, 348-362
- 9 LERNAN, J, PIERCE, F D, and BROGAN, A J Gastric acidity in normal individuals *Jr Clin Investigation*, 1932, xi, 155-165
- 10 WRIGHT, C B Gastric secretion, gastrointestinal motility and position of the stomach in a group of 250 children of the Lymanhurst School, *Arch Int Med*, 1924, xxviii, 435-438
- 11 HERTZ, P Magenuntersuchungen bei jungen Kindern, *Acta Paediat* 1921 1, 298-309
- 12 JACOBSEN, A T B Some investigations on the gastric secretions in children between one and four years of age with gastrointestinal diseases, remarks on treatment, *Ugeskr f Laeger Kobenh*, 1919, lxxxi, 863-873, *Acta med Scandinav*, 1920, lii, 773-790
- 13 HESS, A F The gastric secretion of infants at birth, *Am Jr Dis Child*, 1913 vi, 264-276

- 14 CARLSON, A J The secretion of gastric juice in health and disease, *Physiol Rev*, 1923, iii, 1-40
- 15 DAUWE, F L'hérédité normale et pathologique des fonctions sécrétoires de l'estomac, *Archiv Medic Belg*, 1920, lxxiii, 578
- 16 MARTINEZ, F Familial gastric achylia, *Abstr*, Jr Am Med Assoc, 1927, lxxxviii, 1525
- 17 APPERLY, F L, and NORRIS, J H Familial influence in gastric function, *Brit Med Jr*, 1931, i, 255-258
- 18 EHRLMAN, R Die Bedeutung des Probefrühstücks, *Deutsch med Wchnschr*, 1929, iv, 431-433
- 19 MARTIUS, F Achylia gastrica, ihre Ursachen und ihre Folgen, mit einem anatomischen Beitrage von O Lubarsch, *Publ Franz Deuticke, Leipzig u Wien*, 1897
- 20 FABER, K The etiology and pathogenesis of achylia gastrica, *Am Jr Med Sci*, 1926, clxxii, 1-11
- 21 HURST, A F Schorstein lecture on precursors of carcinoma of stomach, *Lancet*, 1929, ii, 1023-1028
- 22 DEDICHEN, L Anacidity in old persons, *Acta med Scandinav*, 1924, vii, 345-350
- 23 DAVIES, D T, and JAMES, T G I Achlorhydria and anemia in advancing years, *Lancet*, 1930, ii, 899-901
- 24 RAFSKY, H A Discussion, Jr Am Med Assoc, 1931, xcvi, 1220
- 25 BOAS, I Vierzig Jahre Probefrühstück, *Deutsch med Wchnschr*, 1925, i, 976-978
- 26 ISAAK-KRIEGER, K Zur Frage der klinischen Brauchbarkeit der sekretionsprüfung des Magens mit der Verweilsonde, *Arch f Verdauungskkr*, 1926, xxxvii, 442-454
- 27 ANDRESEN, A F R The interpretation of gastric analyses, *N Y State Jr Med*, 1929, xxix, 1497-1503
- 28 GARBAT, A L Clear fluid test meals (water, caffeine solution, alcohol) for use in fractional gastric analysis, *Arch Int Med*, 1931, xlvii, 601-611
- 29 GAITHER, E H Diagnostic value of secretory function in gastric disease various methods studied and compared, *ANN INT MED*, 1932, v, 992-996
- 30 SMITHIES, F A new motor meal and lavage tube, Jr Am Med Assoc, 1914, lxii, 453-454
- 31 ORLOWSKY, W Recherches sur la fonction sécrétoire de l'estomac chez l'homme, *Ann de Med*, 1928, xxiii, 277-291

COEXISTENCE OF PERNICIOUS ANEMIA AND LESIONS OF THE GASTROINTESTINAL TRACT *

I CARCINOMA OF THE STOMACH

Consideration of Twenty Cases Eleven Reported

By H MILTON CONNER, M D , F A C P ,

Rochester, Minnesota

and

IVAR W BIRKELAND,† M D , F A C P ,

Seattle, Washington

REVIEW OF LITERATURE

QUINCKE,¹ in 1876, first mentioned the coexistence of carcinoma of the stomach and progressive pernicious anemia. Since that time, various cases in which there was coexistence of the two diseases have been reported.

It has long been difficult to distinguish certain cases of carcinoma of the stomach from pernicious anemia, since weakness, anorexia, gastric symptoms, insidious onset, and anemia are common to both conditions. The not uncommon absence of gastric symptoms and the occasional yellowish pallor in carcinoma, the not very uncommon severe loss of weight in pernicious anemia, and the occasional red bone marrow due to metastasis in carcinoma, serve to confuse the picture. Probably the two most important clinical characteristics that distinguish pernicious anemia from carcinoma of the stomach are sore tongue, and paresthesia and neurologic symptoms that suggest subacute combined degeneration of the posterior and lateral columns of the spinal cord. Diarrhea occurs much more commonly in pernicious anemia than in carcinoma.

The anemia of carcinoma of the stomach usually is of the hypochromic secondary type, but occasionally it is hyperchromic, such as that of pernicious anemia. Macrocytosis and high hemoglobin index and volume index strongly indicate pernicious anemia, although they are not absolutely diagnostic. Usually leukopenia is present in pernicious anemia, and ordinarily leukocytosis is present in carcinoma of the stomach. The usual relative lymphocytosis and the shift to the right of the polymorphonuclear leukocytes in pernicious anemia, and the presence of the so-called neutrophil of pernicious anemia are of considerable value in the diagnosis. Achlorhydria, present in practically every case of pernicious anemia, is found in only 50

* Submitted for publication November 29, 1932. From The Mayo Clinic, Rochester, Minnesota.

† Formerly a Fellow in Medicine, The Mayo Foundation.

or 60 per cent of cases of carcinoma of the stomach. To confuse the picture, myelocytes may occur in some cases in which carcinoma has invaded the bone marrow, and they may be present in some severe cases of pernicious anemia.

When the best criteria for distinguishing the two diseases are applied, there remain a few cases in which they are apparently coexistent. A number of cases has been reported, particularly in recent years. Some of these seem only to be cases in which the blood picture resembling pernicious anemia accompanies carcinoma of the stomach. In other cases apparently, the two diseases actually coexist, or there has been a consecutive development of the two.

One must distinguish between true cryptogenetic pernicious anemia and the blood picture resembling pernicious anemia, which may be so closely simulated at times by other diseases, particularly by sprue, and, as we have mentioned, occasionally by carcinoma. A perfect picture of pernicious anemia is represented by glossitis, paresthesia, and other evidences of degeneration of the spinal cord, diarrhea, little if any loss of weight, lemon yellow skin, increased hemoglobin index, increased volume index, marked general macrocytosis, leukopenia, relative lymphocytosis, presence of the "polymorphonuclear leukocyte of pernicious anemia," shift to the right of the neutrophils, decrease in platelets, increase in serum bilirubin, presence of urobilin and urobilinogen in the urine and their increase in the stool or duodenal contents, achlorhydria, response to treatment with liver or to the ingestion of gastric tissue, and the occurrence of remissions. One or more of these features may be lacking and still a diagnosis of true pernicious anemia may be entirely tenable. If most of these features are present in an individual case and carcinoma of the stomach is demonstrated either by roentgen-rays, by operation, or by necropsy, the two diseases will usually coexist.

There are several hypotheses as to the coexistence of these diseases. Most observers maintain that pernicious anemia and carcinoma coexist accidentally.^{2, 3, 4, 5, 6, 7, 8, 9, 10} Fischer-Defoy and Lubarsch¹¹ think the coexistence accidental in some instances, and Naegeli,¹² and Bloch¹³ believe this the usual explanation. Other observers believe that the blood picture of pernicious anemia may occur as a result of carcinoma of the stomach.^{14, 15, 16, 17, 18} Fischer-Defoy and Lubarsch, Lazarus,¹⁹ and Brandes²⁰ believe this is true in some instances. Some of this latter group of observers believe that actual pernicious anemia develops as a result of carcinoma of the stomach, others that only the blood picture of pernicious anemia occurs and that true pernicious anemia does not result from carcinoma of the stomach. Among the latter are Fischer-Defoy and Lubarsch, Pappenheim, and Zadek. Naegeli, Bloch, and Minot²¹ believe it possible that the carcinoma develops on soil of pernicious anemia. Brandes, and Lazarus thought this the explanation in some cases.

It would be of great interest and value to determine whether pernicious

anemia is much more common among patients with carcinoma of the stomach than among other patients of the same sex and age, or whether carcinoma of the stomach is more common among those who have pernicious anemia than among others. If these points could be determined accurately in a large series of cases, one might learn whether pernicious anemia predisposes to carcinoma of the stomach, or vice versa.

Dunn²² is of the belief, however, that this question cannot be settled in a clinic such as ours, in which the sampling of patients from distant communities is unequal.

Formerly, any form of hyperchromic macrocytic anemia, associated with leukopenia and with relative lymphocytosis, usually was assumed to represent pernicious anemia. However, at present, in addition to the blood picture, the absence of free hydrochloric acid is usually required, and the addition of one or more of the following symptoms is desirable: sore tongue, paresthesia, and diarrhea. In recent years, a great deal of attention has been paid to the character of the polymorphonuclear leukocytes.

Heinrichsdorff in 1912 made a critical review of all cases of the coexistence of the two diseases reported up to that time, and accepted only a few as unquestionable.

Although we shall not attempt to review in detail the previously reported cases it would appear that some of these cases, particularly those recently reported, have had all of the essential diagnostic features of pernicious anemia and carcinoma of the stomach, and, moreover, some of the patients have responded well to treatment with liver, liver extract, and desiccated swine stomach.

A few cases recently reported are those of Waterfield,²³ Cabot,²⁴ Castle,²⁵ Giffin and Bowler,²⁶ Neuburger,²⁷ Plummer and Simpson,²⁸ Simpson,²⁹ Sonnenfeld, Weinberg,³⁰ and Zadek (two cases). Strandell,³¹ in a recent review of 117 cases of pernicious anemia, reported four cases associated with carcinoma of the stomach, Levine and Ladd³² reported one case in 150 cases of pernicious anemia, Panton, Maitland-Jones and Riddoch,³³ none in 117 cases, and Rohner,³⁴ one in 127 cases.

Eisen,³⁵ in a group of 187 cases of carcinoma of the gastrointestinal tract, did not find a case of pernicious anemia, but in 20 of the 79 cases of carcinoma of the stomach the hemoglobin index was 1 to 1.5. Brandes, in a series of 66 cases of pernicious anemia observed from 1911 to 1919, found carcinoma of the stomach in four of 22 cases in which necropsy had been performed.

Neuburger is of the belief that there is an increased incidence of pernicious anemia in families in which carcinoma exists, and von Hoffmann³⁶ holds the same view. Cornell³⁷ thinks that carcinoma of the stomach not infrequently complicates an already existing pernicious anemia. Davidson and Gulland³⁸ (three cases), Hurst,³⁹ Naegeli ("very few"), and Ungley⁴⁰ have seen the occurrence of the two conditions together.

DATA FROM THE MAYO CLINIC

Records of cases from 1925 to 1930, in which pernicious anemia was positively diagnosed or was considered possible, were taken from the files. These records were examined to find in how many cases carcinoma of the stomach was positively diagnosed or was considered possible. All of the records in which both diagnoses had been made or suggested were critically examined to determine in how many both diagnoses were certainly or almost certainly established. Eight records were found which met this requirement.

For the purpose of determining the percentage of cases in which carcinoma of the stomach afflicted patients with pernicious anemia, a smaller subgroup of records was taken. That is, all records from 1928 to 1930, in which pernicious anemia was positively diagnosed or was considered possible were taken from the preceding, larger group. There were 784 of these. The method of examination of the records of this subgroup was considerably more exact and laborious. At the very outset the entire 784 records were critically examined to determine the number in which the diagnosis of pernicious anemia was well established, and in 658, it was found to be certainly or probably established. Of these 658 cases there were four (0.6 per cent) in which the diagnosis of carcinoma of the stomach was established. This figure may differ greatly from that given in other clinics, for reasons stated elsewhere.

Three other cases in which the two diseases coexisted have been added, these occurred in 1931 and 1932 and before 1925. During this same period there were four more cases in which the coexistence of the two diseases was somewhat doubtful. In all four the existence of pernicious anemia was practically certain, but in two the degree of malignancy (of polyps) was only graded 1⁴¹, in one case the diagnosis of malignant polyps (inoperable) was made only by the roentgenologist, and in the fourth case though roentgenograms indicated carcinoma, at a later date another roentgenologic examination elsewhere was reported negative.

Thus, there were 15 cases in which carcinoma of the stomach and pernicious anemia coexisted with more or less certainty. There also were three cases of definitely diagnosed carcinoma, possibly accompanied by pernicious anemia, and one case of malignant polyp possibly accompanied by pernicious anemia. In still another case in which operation was performed at the clinic for carcinoma of the stomach, it is reported four years after operation that the blood now shows most of the characteristics of pernicious anemia except shift of the polymorphonuclear leukocytes to the right, and that the patient has responded to treatment by liver.

In most instances, the diagnosis of pernicious anemia was made by a physician in the Section on Hematology. A definite diagnosis of pernicious anemia is based on the existence of most, if not all, of the significant features of history, general examination, and known laboratory tests, and a

probable diagnosis on the existence of many of these features but the lack of some of the important ones. A definite diagnosis of carcinoma of the stomach is based on demonstration of the disease at operation or necropsy, with or without positive roentgen-ray observations, and a probable diagnosis is based on a positive report by the roentgenologist. It is possible that some cases of pernicious anemia have been overlooked when the diagnosis was frankly carcinoma of the stomach, because an extensive study for pernicious anemia usually was not made in such cases. It seems likely, however, that almost all instances of carcinoma in cases of frank pernicious anemia were discovered, since roentgenologic examination of the stomach is made as a routine in almost all cases of pernicious anemia as a precautionary measure. It is likely that many cases of carcinoma of the stomach were formerly overlooked when roentgen-rays were not used as a routine procedure when the diagnosis of pernicious anemia was evident. A search for carcinoma should be made in cases of pernicious anemia, especially when the patient has lost much weight.

In this paper are included only the 11 cases in which there was definite or probable carcinoma of the stomach in association with definite or probable pernicious anemia. They are reported in the order of importance as examples, rather than chronologically. In six of these cases the sequence of the two diseases as to incidence could not be established. In three the carcinoma seemed to follow the pernicious anemia (by seven years, one and a half years, and seven to eight years). In one case, pernicious anemia was diagnosed 32 months after partial resection of the stomach for carcinoma, although there was some suggestion of pernicious anemia ten months after operation. In another case, pernicious anemia was diagnosed six years after a similar operation, but there was considerable suggestion of its presence before operation.

The series therefore yielded no definite indications as to a fixed sequence of development. The fact that in three cases carcinoma seemed to follow the development of pernicious anemia, and in two cases pernicious anemia apparently followed the development of carcinoma suggests that each disease may possibly predispose to the other. On this basis the apparently simultaneous occurrence of both in six of the cases might not be a matter of mere chance. In any event, the two diseases do not appear to be antagonistic.

When both diseases are present, each disease should be treated as though the other did not exist. Resection of the stomach for carcinoma should not be denied to a patient simply because he also has pernicious anemia, nor should the treatment of pernicious anemia be neglected because of the seriousness of the illness due to carcinoma. The diseases seem to affect each other's progress very little. It seems best, however, to institute radical treatment for pernicious anemia before operation so that neurologic lesions may be prevented and the patient be placed in the best possible condition for operation.

PERNICIOUS ANEMIA AND CARCINOMA OF THE STOMACH
APPARENTLY DEVELOPING ALMOST SIMULTANEOUSLY
(CASES 1 TO 6)

*Case I** A farmer, aged forty-four years, from Colombia, South America, registered January 30, 1932. His mother had died of carcinoma of the stomach, one brother had died of tuberculosis, and a sister of typhus fever. The patient had had influenza in 1919, gonorrhea in 1920, and malaria in 1922. His chief complaints were recurring weakness, epigastric pain, and diarrhea for eighteen months. He noted that his tongue had been red and sore for the last eight months, and that mild numbness had been present in the fingers for the last year. His physician had found that anemia was present, and had prescribed a small amount of liver extract.

The blood pressure, pulse rate, and temperature were normal. The tongue was slightly red and somewhat smooth. The concentration of hemoglobin was 10.2 gm in each 100 cc of blood. The volume index was 1.35. Erythrocytes numbered 2,140,000 and leukocytes 4,600 in each cubic millimeter of blood. In morphologic examination of the blood the following features were noted: normal differential leukocyte count, moderate anisocytosis, slight polychromatophilia, reticulated erythrocytes 15 per cent, macrocytosis without poikilocytosis or stippling, hyperchromasia of individual erythrocytes, and neutrophils designated as of toxic type (grade 2) with large fat lobes, a picture probably not characteristic of pernicious anemia. Urinalysis and serologic test for syphilis were negative. Achlorhydria was found to be complete by the fractional method of analysis. The concentration of bilirubin was 1.7 mg in each 100 cc of serum, and the van den Bergh reaction was indirect. The concentration of calcium was 9.6 mg in each 100 cc of serum. Parasites and ova were absent in three specimens of stool. A roentgenogram of the thorax gave negative results and one of the stomach revealed carcinoma involving the lesser curvature of the middle and upper third. The patient was given 20 cc of a preparation of liver extract intravenously. Four days later the reticulated erythrocytes had risen from 3 to 21.8 per cent.

At operation an extensive polypoid carcinoma of the stomach, with extensive involvement of the lymph nodes was found. The growth was incompletely removed. Recovery was uneventful. In a letter received from a brother, it was stated that the patient died five months after the exploratory operation.

The history of sore tongue, diarrhea, numbness, high hemoglobin index and volume index, and macrocytosis favored a diagnosis of pernicious anemia, but the blood picture was not entirely characteristic, principally because of the character of the leukocytes. Taking into account the patient's residence in the tropics and the presence of macrocytosis, sore tongue, and diarrhea, sprue also was considered. The rapid response of the reticulated erythrocytes following injection of liver extract made the diagnosis of pernicious anemia or sprue (probably pernicious anemia) practically definite. The presence of carcinoma was proved at operation.

Case II A church sexton, aged fifty-seven years, registered May 24, 1930. He complained of weakness, vague epigastric distress, fatigability, palpitation and tachycardia on exertion, anorexia, occasional gaseous dyspepsia, and some burning in the epigastrium which was relieved by ingestion of food. He had lost 15 to 20 pounds in weight. He complained of insomnia, worrying and depression. Vomiting, hematemesis, melena, soreness of mouth or tongue, paresthesia of the extremities, and diarrhea, were not present.

The patient was markedly pale with sallow complexion, he was emaciated and weak. Definite atrophy of the papillae was observed on the edge of the tongue. There was a systolic murmur over the cardiac area. The neurologic examination was

* Unimportant data usually are omitted in reports of cases.

negative The concentration of hemoglobin was 68 gm, erythrocytes numbered 1,100,000, and leukocytes 6,300 The color index was 1.85, the percentages of the various types of leukocytes were as follows lymphocytes 21.5, monocytes 0.5, transitionals 4, neutrophils 71.5, and eosinophils 2.5 The percentage of reticulated erythrocytes was 1.7 The blood smear was characteristic of pernicious anemia Achlorhydria was noted following fractional analysis of a test meal Blood, graded 2, was found in the contents of the stomach A roentgenogram revealed a pedunculated tumor in the median portion of the stomach, which was considered probably malignant and the advisability of operation was thought questionable The diagnosis was pernicious anemia and pedunculated tumor of the stomach

At operation, a polypoid tumor, about 6 cm in diameter, and adjacent nodes were removed The pathologist reported adenocarcinoma, graded 2, with involvement of lymph nodes

Following the administration of liver extract there was a typical response in reticulated erythrocytes which reached a peak of 11.1 per cent When the patient was dismissed, the concentration of hemoglobin was 58 per cent (Dare), erythrocytes numbered 2,780,000, and leukocytes 6,000 Four months later, the concentration of hemoglobin was 66 per cent, erythrocytes numbered 4,270,000, and leukocytes 5,400, the differential count was normal The percentage of reticulated erythrocytes was 0.8 Definite features of pernicious anemia were observed in blood smears, including macrocytosis and a shift to the right in the leukocyte picture The patient made an excellent recovery

Atrophy of the tongue, high hemoglobin index, blood smear characteristic of pernicious anemia, make the presence of pernicious anemia practically definite The presence of carcinoma was proved at operation

Case III A concrete worker, aged fifty-six years, registered at the Clinic August 3, 1926 One brother had died of carcinoma Three months before admission, the patient became weak, lost his appetite, and 23 pounds in weight Mild attacks of belching, a bad taste in the mouth, edema of the ankles, nervousness, worry, and insomnia were present The tongue was not sore and neither diarrhea nor paresthesia was present

The patient was markedly pale, with a lemon yellow tint to the skin and conjunctivae He was moderately emaciated and weak Atrophy of the tongue and dental sepsis were present There was a faint systolic murmur over the cardiac area Evidence was found of a mild peripheral neuritis such as is seen in early involvement of the nerves in pernicious anemia The concentration of hemoglobin was 41 per cent (Dare), erythrocytes numbered 1,830,000 and leukocytes, 8,700 The color index was 1.1+ The percentages of the various types of leukocytes were as follows lymphocytes 35, monocytes 1, transitionals 1, neutrophils 62, and eosinophils 1 The morphologic examination revealed moderate anisocytosis and polychromatophilia, and slight poikilocytosis and basophilic stippling The concentration of bilirubin was 5 mg in each 100 cc of serum, the van den Bergh reaction was direct Achlorhydria was found by the fractional method of analysis Blood (graded 2) was found in the gastric contents Roentgenologic examination gave negative results The diagnosis was pernicious anemia with mild peripheral neuritis

The patient was given three transfusions of blood and died in a severe reaction after the third transfusion

Necropsy revealed the typical changes of pernicious anemia, red bone marrow, hemosiderosis of the liver, fatty changes of the myocardium and slight splenomegaly (264 gm) A carcinoma 4 by 5 cm and a small ulcer on the anterior wall of the stomach were found with metastasis to the regional lymph nodes and omentum There were several acute ulcers of the mucosa of the transverse colon

Lemon yellow skin and sclerae atrophy of the tongue, peripheral neuritis, high color index, necropsy findings of pernicious anemia, including enlarged spleen, make

the presence of pernicious anemia almost certain Treatment with liver was not then in use Carcinoma was found at necropsy

Case IV. A carpenter, aged fifty-nine years, registered May 4, 1929 He had had an incision of a perianal abscess ten years previously He had been weak, pale, and nervous since Constipation had been present for five years, and anorexia for two and a half years, following an attack of bronchitis Roentgenograms of the stomach had twice given negative results Eighteen months prior to registration the erythrocyte count was 1,000,000 He had been given liver, and liver extract and a transfusion of blood and had improved temporarily For the last year there had been a cotton-like sensation in the soles of his feet, but neither soreness of the tongue nor diarrhea had been noted During the last six months his condition had grown definitely worse

The patient was yellowish pale, markedly weak, and prematurely senile A generalized coarse tremor and evidence of subacute, combined degeneration of the posterior and lateral columns of the spinal cord were present The concentration of hemoglobin was 51 per cent, the erythrocytes numbered 2,700,000 and the leukocytes 7,500 The color index was 0.9+ The percentages of the various types of leukocytes were as follows lymphocytes 30, monocytes 1, transitionals 1.5, neutrophils 62.5, eosinophils 4, and basophils 1 The percentage of reticulated erythrocytes was 0.9 The blood smear was characteristic of pernicious anemia The presence of achlorhydria was proved by the histamine method There was a moderate amount of fresh blood in the gastric contents Roentgenograms revealed the presence of a polypoid tumor on the posterior wall of the middle third of the stomach, whether malignant or benign could not be determined, and partial destruction of the third rib on the right side, suggestive of osteitis fibrosa cystica The diagnosis was pernicious anemia with combined sclerosis of the spinal cord, polypoid tumor of the stomach, and questionable metastasis to the third rib

At operation, a pedunculated papillary tumor about 4 cm in diameter was excised from the posterior wall of the stomach, also a small nodule 2.5 cm distant from the main mass The pathologist reported that the polyp (2.5 by 0.5 cm) and the nodule (1 cm) were adenocarcinomatous, both graded 2+ Following operation, the patient went into shock Solutions of acacia and of glucose were given intravenously, blood transfusion was carried out, and the oxygen tent was used, all without success Permission for necropsy was refused

The yellowish pallor, remission of symptoms after liver extract, blood smear picture, paresthesia, combined degeneration of the posterior and lateral columns of the spinal cord, supported the diagnosis of pernicious anemia The presence of carcinoma was proved at operation

Case V A farmer, aged sixty-six years, registered February 27, 1930 His family history was essentially negative He complained of an infected toe, of dizziness, and of buzzing in the left ear Slight irregularity in the bowel movements had been noted but diarrhea, bloody or tarry stools had not been observed The concentration of hemoglobin was 15.2 gm and the erythrocytes numbered 3,700,000 The patient returned September 10, 1931 because of loss of weight, sore tongue, anorexia, and tingling and swelling of the feet

The blood pressure, pulse rate and temperature were normal The patient was emaciated The tongue was smooth The thorax and abdomen were normal The concentration of hemoglobin was 9.7 gm, erythrocytes numbered 2,350,000 and leukocytes 10,700 in each cubic millimeter of blood A blood smear was characteristic of pernicious anemia Basophilic stippling and an occasional Howell-Jolly body were observed The differential count was normal Neutrophils were of the toxic type, graded 3 The percentage of reticulated erythrocytes was 1.7 Achlorhydria was found by fractional analysis of a test meal The urinalysis was negative A roent-

genogram revealed the presence of a large, hard intragastric tumor at the pyloric end of the stomach, and a normal thorax

Partial gastrectomy was performed, a polypoid carcinoma about 6 cm in diameter was found involving the antrum. The patient made a good recovery and was given from 2 to 6 vials of liver extract daily, and one transfusion of blood. Unfortunately, estimation of reticulated erythrocytes was not made often enough to determine their course. When the patient was dismissed the concentration of hemoglobin was 52 per cent, erythrocytes numbered 2,480,000 and leukocytes, 5,300.

A letter from the patient's widow stated that he died two and a half months after the operation. For a month after operation he took one-half pound of liver daily.

The achlorhydria, the blood picture, history of sore tongue, and appearance of tongue at the time of examination, indicated pernicious anemia. Operation established the diagnosis of carcinoma of the stomach. It seems unlikely that the characteristic blood picture and sore tongue were due to carcinoma of the stomach. The patient probably died as a result of carcinoma, although his failure to take liver during the last six weeks of his life suggests that pernicious anemia may have been a contributing cause.

Case VI A laborer, aged sixty-one years, registered June 30, 1930. During the previous year he had been weak, and fatigued, with indefinite sore tongue, following treatment for anemia with liver extract he improved temporarily. For the last two months, dyspnea on exertion, increasing constipation, gaseous distention, and dull pain in the abdomen had occurred. Neither nausea, vomiting, diarrhea, nor paresthesia had been present, but the tongue was sore at the time of admission.

The patient was pale. The abdomen was distended. Ascites, an ulcerative process about the umbilicus, and an irregular mass in the upper part of the abdomen were observed. The concentration of hemoglobin was 79 gm, erythrocytes numbered 1,600,000, and leukocytes 9,900 in each cubic millimeter of blood. The percentages of the various types of leukocytes were as follows: lymphocytes 23.5, monocytes 1.5, transitionals 2.5, neutrophils 70.5, and eosinophils 2.5. A blood smear was characteristic of pernicious anemia. Achlorhydria was found following fractional analysis of a test meal. There was no blood in the gastric contents. Roentgenograms revealed the presence of a carcinoma of the lower third of the stomach and bilateral infiltration of the lungs, considered metastatic. The diagnosis was pernicious anemia and carcinoma of the stomach with metastasis to the lungs. The patient returned home and died three weeks later. Necropsy was not performed.

High index of hemoglobin, sore tongue, characteristic blood smear picture, and response to liver extract supported a diagnosis of pernicious anemia. Carcinoma of the stomach was practically proved by the mass in the abdomen, and by roentgenograms of stomach and lungs.

PERNICIOUS ANEMIA APPARENTLY FOLLOWING CARCINOMA OF THE STOMACH (CASES 7 AND 8)

Case VII A housewife, aged forty-seven years, registered September 4, 1920, complaining of stomach trouble and weakness. Her mother had died of carcinoma of the breast. The patient had had diarrhea since childhood. For ten years, periodic indigestion, pain in the abdomen two or three hours after meals, nausea with suggestive relief from soda, and pain in the abdomen at night had been present. Six or seven months previously the Sippy diet had given relief. A short time before admission, the symptoms returned and she vomited fresh blood. There had been intermittent soreness of the tongue but no paresthesia.

The patient was well nourished, with moderate pallor and weakness. A mass was present in the upper left side of the abdomen. Stomatitis and glossitis were present. The concentration of hemoglobin was 40 per cent, erythrocytes numbered 3,200,000.

and leukocytes 5,000 The color index was $0.6+$ The percentages of the various types of leukocytes were as follows lymphocytes 32.5, neutrophils 63.5, eosinophils 3, and basophils 1 In morphologic study of the blood, the following features were noted slight anisocytosis, poikilocytosis, and polychromatophilia There was occult blood in the stools Achlorhydria was found by the fractional method of analysis There was no blood in the gastric contents Carcinoma of stomach of questionable operability was revealed by roentgen-rays The diagnosis was carcinoma of the stomach and secondary anemia

At operation, a large, ulcerated, necrotic and very malodorous carcinoma was found on the posterior wall of the stomach above the incisura, completely encircling the stomach with extensive involvement of the omentum Two-thirds of the stomach above the incisura was resected, 25 cm of the pyloric end and the dome of the stomach were preserved The pathologist reported carcinoma, 12 by 11 by 5 cm, without involvement of the lymph nodes Treatment by irradiation was given several times during the next four years The patient had attacks of diarrhea, soreness of the tongue, and transient numbness of the fingers, and one attack each of arthritis and cystitis, she was constantly pale and her weakness was gradually increasing

When the patient was readmitted, November 24, 1926, examination revealed extreme weakness and pallor, ecchymoses under the tongue, a palpable spleen, questionable enlargement of the liver, and slight edema of the ankles The concentration of hemoglobin was 31 per cent, erythrocytes numbered 1,440,000 and leukocytes 3,200 The color index was $1.0+$ The percentages of the various types of leukocytes were as follows lymphocytes 42.5, monocytes 3.5, transitionals 1.5, neutrophils 51, eosinophils 1, and basophils 0.5 The volume index was 0.94 Morphologic study revealed moderate anisocytosis and poikilocytosis, and slight polychromatophilia and basophilic stippling Achlorhydria was noted following analysis of a simple Ewald meal There was no blood in the gastric contents Roentgenograms revealed that carcinoma had not recurred and that there was no evidence of metastasis to the thorax or bones A diagnosis of pernicious anemia was made

Transfusions of blood and dilute hydrochloric acid and liver were given At dismissal, the concentration of hemoglobin was 70 per cent, erythrocytes numbered 3,140,000 and leukocytes 6,600 The color index was $1.1+$ and the volume index 1.13

A letter from the patient three years later stated that she had improved, good health had been maintained, and blood counts were normal Another letter was received five years later, but nothing was said regarding her health

Diarrhea, soreness of tongue, stomatitis, glossitis, numbness of fingers, increased hemoglobin index late in the disease, response to treatment by liver (this patient also was given transfusions) indicated pernicious anemia The presence of carcinoma of stomach was proved at operation Definite evidence of pernicious anemia developed six years after removal of two-thirds of the stomach for carcinoma, although there was considerable suggestion of it in the stomatitis and glossitis before operation Whether the operation was a factor in the development of the pernicious anemia must remain conjectural

Case VIII A housewife, aged fifty-three years, registered October 2, 1926, complaining of anemia and weakness She had had symptoms typical of peptic ulcer with vomiting for the preceding twelve years Eight years previously she had had "flu" and weakness and pallor afterward, with increase in weakness, fatigability and dyspnea on exertion in the last year, but without loss of weight, soreness of mouth or tongue, diarrhea or paresthesia She had been treated with iron, raw beef, sunlight, and what she called serum

The patient was markedly pale, with a lemon yellow tint The tongue was normal There was a mass in the mid-epigastrium The concentration of hemoglobin was 27 per cent Erythrocytes numbered 3,080,000 and leukocytes 4,800 The color index was $0.4+$ The percentages of the various types of leukocytes were as follows

lymphocytes 33.5, transitionals 2, neutrophils 59, eosinophils 3, and basophils 1.5. Morphologic examination of the blood revealed moderate poikilocytosis and slight anisocytosis and polychromatophilia. Achlorhydria was observed in an analysis of a fractional test meal. There was a trace of blood in the gastric contents. A roentgenogram disclosed the presence of a tumor, considered benign, on the posterior wall of the middle third of the stomach. Diagnosis was benign tumor of the stomach and severe secondary anemia.

At operation, a pedunculated tumor, about 3 cm in diameter, was excised. The pathologist reported a pedunculated adenoma containing an adenocarcinoma graded 2.

The patient returned ten months later for a check-up. She still tired easily, was free of gastric symptoms, but had intermittent tingling of hands and feet. Neither soreness of the mouth or tongue, nor diarrhea was present. The concentration of hemoglobin was 62 per cent, erythrocytes numbered 3,710,000 and leukocytes 7,700. The color index was 0.8+. The percentages of the various types of leukocytes were as follows: lymphocytes 29.5, monocytes 2, transitionals 3, neutrophils 59, eosinophils 4.5, and basophils 2. In morphologic studies of the blood the following were noted: slight anisocytosis, slight poikilocytosis, and slight polychromatophilia. Achlorhydria was found by the fractional method of analysis. There was no blood in the gastric contents. A roentgenogram of the stomach did not reveal recurrence. Dilute hydrochloric acid and a diet high in vitamins were prescribed.

Twenty-two months later the patient again returned because of increasing constant numbness of the feet and hands. Moderate pallor and evidence of definite subacute combined sclerosis of the spinal cord were noted. The concentration of hemoglobin was 68 per cent, erythrocytes numbered 2,070,000 and leukocytes 5,400. The color index was 1.2+. A blood smear picture was characteristic of pernicious anemia. Achlorhydria was found by the fractional method of analysis. After liver or liver extract and dilute hydrochloric acid had been taken for one month the concentration of hemoglobin was 58 per cent, erythrocytes numbered 3,190,000 and leukocytes 6,100. The color index was 0.9+, and there was slight lymphocytosis.

The patient returned June 11, 1931. She had not been taking liver extract regularly. The numbness and weakness had become worse. Examination revealed evidence of marked combined degeneration of the posterior and lateral columns of the spinal cord. The concentration of hemoglobin was 59 per cent, erythrocytes numbered 1,990,000 and leukocytes 5,900. The differential count was normal. A blood smear was characteristic of pernicious anemia. The patient was instructed to use 6 vials of liver extract No. 343 daily. The last report showed that the erythrocytes numbered 3,500,000 and the concentration of hemoglobin was 68 per cent.

The anemia was of the hypochromic secondary type before operation, but ten months after operation numbness and tingling were present and thirty-two months after operation there was a definite blood picture of pernicious anemia. Whether the pernicious anemia was developing before operation, coexistent with the gastric lesion, or whether it occurred as a result of partial gastrectomy cannot be determined, but the former hypothesis seems more plausible. Adenocarcinoma graded 2 was demonstrated at operation, but the fact that the patient was living five years after operation suggests that the lesion was only mildly malignant or that removal was absolutely complete.

CARCINOMA OF THE STOMACH APPARENTLY DEVELOPING AFTER PERNICIOUS ANEMIA (CASES 9 TO 11)

Case IX A physician, aged fifty-three years, registered June 27, 1923. The family history was not significant. His chief complaint was of general weakness. He had had influenza in 1918, pulmonary tuberculosis in 1919, and malaria in 1921.

Following this his skin became yellow and anemia developed with a concentration of hemoglobin of 43 per cent and erythrocytes numbering 1,700,000. The tongue had been a little sore. The erythrocyte count increased to 4,000,000 in 1922, but in March, 1923, loss of weight, discomfort in the stomach and bowels, nausea and anorexia developed.

At examination the skin had a lemon tint. The concentration of hemoglobin was 47 per cent, erythrocytes numbered 1,850,000, and leukocytes 3,600. The color index was 1.2. The differential count was normal. In morphologic study of the blood the following features were noted: moderate anisocytosis, slight poikilocytosis, basophilic stippling, and polychromatophilia. The percentage of reticulated erythrocytes was 2.4. Achlorhydria was found by the fractional test of an Ewald meal. The Wassermann reaction was negative. Urinalysis was negative except for a slight trace of urobilin and urobilinogen. Malarial parasites were absent. Roentgenograms revealed the presence of an old lesion in the apex of the right lung and of a normal stomach and gall-bladder. Following the use of hydrochloric acid and Fowler's solution, drainage of the duodenum, flushing of the bowel, and two transfusions of blood, the concentration of hemoglobin rose to 77 per cent and the erythrocyte count to 4,280,000.

In April, 1924, palpitation, dyspnea, slight edema of the ankles, constipation, considerable soreness at the right costal margin, occasional sore tongue, and slight numbness and tingling in the hands and feet occurred. At examination June 17 the tongue was smooth, and the color lemon yellow. The concentration of hemoglobin was 35 per cent, erythrocytes numbered 1,370,000, and leukocytes 2,400. The color index was 1.2. Occasional normoblasts were noted. The differential count was essentially normal. Morphologic studies revealed moderate anisocytosis and slight poikilocytosis and polychromatophilia. Achlorhydria was found by the fractional method of analysis. Transfusions, Fowler's solution, and hydrochloric acid were given. Following treatment the concentration of hemoglobin was 73 per cent, erythrocytes numbered 3,070,000 and leukocytes 3,400.

The patient returned July 14, 1925. He had become easily fatigued, but neither sore tongue nor diarrhea had developed. The paresthesia had disappeared. Soreness in the region of the gall-bladder was still present. Moderate pallor was noted. Prostatitis (graded 2) was found. The blood pressure, pulse rate and temperature were normal. The concentration of hemoglobin was 44 per cent, erythrocytes numbered 2,480,000, and leukocytes 5,100. Morphologic studies showed the presence of moderate anisocytosis and poikilocytosis, and slight basophilic stippling and polychromatophilia. The differential count was normal except for the presence of 7.5 per cent of eosinophils. A roentgenogram did not reveal the gall-bladder. Hepatic function, serum bilirubin, and concentration of blood urea were normal. The prostatitis was treated and the tonsils were removed.

The patient returned July 12, 1926. He had felt well until a month previous when nausea and a distaste for food suddenly developed. He had had an occasional attack of pain in the right subcostal region with distention, belching and heartburn, for which he had had the gall-bladder drained. He also had had an attack of precordial and substernal pain radiating down the left arm. Except for pallor and absent knee and ankle reflexes, general examination gave essentially negative results. The concentration of hemoglobin was 25 per cent, erythrocytes numbered 1,100,000 and leukocytes 4,650. The hemoglobin index was 1.1. Transfusions, hydrochloric acid, Fowler's solution, and a few doses of gentian violet by mouth were given. Following treatment the concentration of hemoglobin was 42 per cent and the erythrocyte count was 2,890,000.

The patient again returned, September 1, 1930. He had been taking liver during the previous four years and had been doing well, working every day, and had had no characteristic symptoms. General examination was essentially negative. The con-

centration of hemoglobin was 15.2 gm, erythrocytes numbered 4,110,000 and leukocytes 3,700. Lymphocytosis was relatively marked, and macrocytosis was definite, but there was no right shift in the polymorphonuclear leukocytes. A test meal showed fresh blood in the stomach. A roentgenogram of the stomach was negative. It was advised that another roentgenogram of the stomach should be made at an early date.

The patient returned July 10, 1931. Two months after his previous return home he had taken a test meal which revealed blood, and had had a roentgenogram made of the stomach, which had been pronounced negative. In February 1931, following influenza, the concentration of hemoglobin had been 29 per cent and the erythrocytes had numbered 2,000,000. In May 1931, he had vomited blood, and a roentgenogram had indicated an obstruction in the esophagus. There had been a little difficulty in swallowing. An increased amount of liver, liver extract, and ventriculin improved the condition of the blood, but loss of weight continued.

General examination was negative except for the pallor. The concentration of hemoglobin was 9 gm, erythrocytes numbered 3,540,000 and leukocytes 5,700. Morphologic studies revealed the following: slight poikilocytosis, anisocytosis, and polychromatophilia. Platelets numbered 184,000 and reticulated erythrocytes 1.4 per cent. There was little evidence of pernicious anemia in blood smears. Polymorphonuclear leukocytes were of the toxic type, graded 1 to 2. The serologic test for syphilis was negative. Complete achlorhydria was proved by a fractional analysis of a test meal. A trace of blood in the gastric contents and occult blood in the stools were noted. A roentgenogram revealed the presence of a carcinoma involving the lower end of the esophagus and the cardiac end of the stomach. After surgical consultation, the patient was advised not to undergo operation. He was told that dilatation or gastrostomy might be necessary if the esophagus became completely obstructed.

Yellowish pallor, sore tongue, frequent remissions and relapses, moderately high hemoglobin index, urobilin and urobilinogen in urine, numbness and tingling, macrocytosis, improvement following the liver extract and ventriculin make the diagnosis of pernicious anemia almost positive. The presence of a carcinoma in the stomach was revealed by repeated blood in the gastric contents and stools, and by roentgenograms, seven to eight years after the apparent onset of pernicious anemia.

Case X A real estate agent, aged fifty-six years, registered August 19, 1919. One brother had died of carcinoma of the stomach. The patient had lost 30 pounds in weight, he was pale, sore in various parts of the abdomen, and had attacks of weakness.

At examination marked pallor was noted. The spleen was palpable. The concentration of hemoglobin was 49 per cent, erythrocytes numbered 2,240,000 and leukocytes 4,200. The color index was 1.1. The differential count was normal. Morphologic study revealed moderate anisocytosis and poikilocytosis. Achlorhydria was observed following fractional analysis of a simple Ewald meal. Two roentgenograms of the stomach gave negative results. The diagnosis was probable pernicious anemia. Anemia progressed rapidly and a few days later the concentration of hemoglobin was 40 per cent, erythrocytes numbered 1,590,000, and the color index was 1.2+. Improvement occurred following two transfusions of blood, and the taking of Fowler's solution and Blaud's pills.

The patient returned to the Clinic March 16, 1923. Six months before, numbness and tingling had occurred in the hands and feet and the anemia had recurred. There were a few cracks in the tongue and moderate pallor. The concentration of hemoglobin was 64 per cent, erythrocytes numbered 2,480,000 and leukocytes 4,400. He was given two transfusions of blood, dilute hydrochloric acid, Fowler's solution, and Blaud's pills.

The patient again came to the Clinic three and a half years later because of anemia, a "load on his stomach," anorexia, weakness and some numbness in hands and feet. No soreness of the tongue or diarrhea had been noted.

Examination revealed loss of strength (graded 2), xerotic skin and an irregular mass in the left portion of the epigastrium. The concentration of hemoglobin was 75 per cent, erythrocytes numbered 4,390,000 and leukocytes 10,500. The differential count was normal. A roentgenogram of the stomach revealed carcinoma of the pyloric end, with fairly marked obstruction, probably operable. The diagnosis was carcinoma of the stomach, and pernicious anemia with peripheral neuritis.

At operation a perforating type of carcinoma of the pyloric end of the stomach, with extensive implants in the gastrocolic omentum and several small nodules in the liver were discovered. Posterior gastroenterostomy was done. Twelve days after operation, gastric retention, gradual failure, and coma led to death. Necropsy revealed carcinoma of the pyloric end of the stomach with metastasis to the peritoneum, regional lymph nodes, pancreas and liver, multiple polyps of the stomach, generalized peritonitis and septic splenomegaly.

A high hemoglobin index, remission, paresthesia, peripheral neuritis, and the condition of the tongue make a diagnosis of pernicious anemia almost positive. Carcinoma was found at operation. Evidence of carcinoma did not appear until seven and a half years after the discovery of pernicious anemia.

*Case XI** A farmer, aged fifty-two years, registered May 5, 1915. About a year previously hemorrhoidectomy had been performed because of mucus and blood in the stools. Cramps in the lower part of the abdomen, gas, nausea, vomiting, constipation, bloody and watery stools, and bearing down in the rectum soon developed, and the patient's appetite became poor.

At examination the patient was pale. Edema was absent. There was a systolic murmur at the apex. External hemorrhoids (graded 2) were found. The concentration of hemoglobin was 30 per cent, erythrocytes numbered 1,300,000 and leukocytes 4,700. The color index was 1.1. The percentages of the various types of leukocytes were as follows: polymorphonuclears 53, lymphocytes 39.3, eosinophils 7, basophils 0.3 and neutrophilic myelocytes 0.3. Morphologic studies revealed marked anisocytosis, and slight poikilocytosis, granular degeneration, and polychromatophilia. *Endamebae histolyticae* were discovered in the stools. Urinalysis, Wassermann reaction of the blood, and proctoscopic examination were negative. Pernicious anemia, and infection with amebae were diagnosed, and arsenic, iron, emetin, and enemas of coal oil were given.

The patient returned November 15, 1916, with improvement in strength and color. Numbness in the fingers, and weakness had developed. There was a rectal discharge of mucus. Pain in the abdomen had been general. Severe diarrhea had developed, with fresh blood in the stool. There was a gnawing sensation in the epigastrium which was relieved by the ingestion of food. Nocturia, anorexia, sore mouth, dry and "beefy" tongue, and loss of weight were present.

The blood pressure was 92 systolic and 50 diastolic in millimeters of mercury. The pulse rate was 88 beats each minute. A round mass approximately 3 cm in diameter was present just below the left costal margin, which moved with respiration. The liver edge was palpable 5 cm below the costal margin. The spleen was palpable, and the right lower part of the thorax was tender. Hemorrhoids (graded 2), albumin (graded 2), and hyaline casts (graded 2) were present. There was an occasional pus cell in the urine. Achlorhydria was observed following fractional analysis of an Ewald meal. The concentration of hemoglobin was 60 per cent, erythrocytes numbered 2,850,000 and leukocytes 9,500. The differential count was normal except for 10 per cent of eosinophils. A roentgenogram revealed the presence of an inoperable carcinoma of the stomach. Neurologic examination indicated involvement of the posterior columns of the spinal cord. Diagnosis was inoperable carcinoma of the stomach with pernicious anemia. The patient died November 22, 1922 at his home. Necropsy was not performed.

* Reported by Giffin and Bowler.

The history of diarrhea, soreness of mouth, beefy red tongue with anemia, high index of hemoglobin, and evidence of neurologic involvement make the diagnosis of pernicious anemia practically certain. A roentgenogram of the stomach gave definite evidence of carcinoma. Operation and necropsy were not performed. Evidence of carcinoma did not appear until one and a half years after the appearance of pernicious anemia.

SUMMARY

Carcinoma of the stomach and pernicious anemia may coexist. Either disease may occur first, but in most instances their occurrence appeared to be simultaneous, and a definite sequence was not established in this study.

In 11 cases, the coexistence was certain or almost certain, and these cases are reported. In four the coexistence was somewhat doubtful, and in five other cases the occurrence of both diseases together was possible.

Each disease should be treated as if it existed alone. The specific treatment for pernicious anemia should be instituted before operation for carcinoma, in order to avoid serious consequences from the anemia, and to forestall if possible neurologic complications.

BIBLIOGRAPHY

- 1 QUINCKE, quoted by DEVIC, E., and TOLON, G. Cancer de l'estomac a forme d'anemie pernicieuse, l'anemie pernicieuse progressive est-elle une entite clinique? *Lyon Méd*, 1904, cii, 453-464.
- 2 ARNETH, quoted by HEINRICHSORFF.
- 3 CABOT, R. C. Pernicious anemia: a study of one hundred ten cases, *Am Jr Med Sci*, 1900, cxx, 139-149.
- 4 CABOT, R. C. Pernicious and secondary anemia, chlorosis and leukemia, *In* OSLER, W. *Modern medicine*, 1927, Lea and Febiger, Philadelphia, v, 33-100.
- 5 EHRLICH, quoted by CABOT.³
- 6 HOUSTON, T. The conditions that simulate pernicious anemia, *Brit Med Jr*, 1903, ii, 1257-1261.
- 7 KRUKIEWICZ, A., quoted by FISCHER-DEFOY and LUBARSCH.
- 8 NAUER, quoted by STEMPERLIN, O. Zur Differentialdiagnose der perniziösen Anämie, *Med Klin*, 1908, iv, 667-670.
- 9 VON NOORDEN, quoted by ZADEK.
- 10 SONNENFELD, A. Perniciöse Anämie und Karzinom, *Deutsch med Wchnschr*, 1924, 1, 1794-1796.
- 11 FISCHER-DEFOY, W., and LUBARSCH, O. Pathologie des Karzinoms, *Ergebn d allg Path u path Anat*, 1904-1905, x, 850-950.
- 12 NAEGELI, quoted by HIRSCHFELD.
- 13 BLOCH, E. Zur Klinik und Pathologie der Biermer'schen progressiven Anämie, *Deutsch Arch f klin Med*, 1903, lxxvii, 277-307.
- 14 HEINRICHSORFF, A. Über die Beziehungen der perniziösen Anämie zum Karzinom, *Folia haematol*, *Arch*, 1912, xiv, 359-429.
- 15 HIRSCHFELD, H. Carcinom und perniziöse Anämie, *Ztschr f Krebsforsch*, 1912, xi, 376-387.
- 16 HURST, A. F. The pathogenesis of subacute combined degeneration of the spinal cord with special reference to its connection with Addison's (pernicious) anemia, achlorhydria, and intestinal infection, *Brain*, 1925, xliii, 218-232.
- 17 PAPPENHEIM, A. Perniciöse Anämie und Karzinom in ihren gegenseitigen Beziehungen, *Folia haematol*, *Arch*, 1912, xiv, 329-358.
- 18 ZADEK, J. Beiträge zur Aetiologie, Klinik und Hamatologie der perniziösen Anämie, *Berl klin Wchnschr*, 1917, liv, 1253-1259.

- 19 LAZARUS, A Diseases of the blood, *In* NOTHNAGEL Encyclopedia of practical medicine, 1904, W B Saunders Co, Philadelphia
- 20 BRANDES, T Über die Beziehungen der perniziösen Anämie zum Magen-carcinom, *Med Klin*, 1921, xvii, 193-196
- 21 MINOT, G R Clinical discussion of the anemias, *In* Oxford Medicine, 1920, Oxford University Press, ii, 589-679
- 22 DUNN, H F Personal communication to the authors
- 23 WATERFIELD, R L Addison's anemia with subacute combined degeneration of the spinal cord secondary to cancer of the stomach, *Guy's Hosp Rep*, 1923, lxxiii, 208-210
- 24 CABOT, R C Case records Case 14,442 Development of gastric symptoms in a patient totally relieved of pernicious anemia by liver therapy, *New Eng Jr Med*, 1928, cxcix, 1274-1276
- 25 CASTLE, W B The etiological relationship of achylia gastrica to pernicious anemia, *Proc Roy Soc Med, Sect Med*, 1929, xxii, 58-60
- 26 GIFFIN, H Z, and BOWLER, J P Diseases which may be associated with pernicious anemia, *Minnesota Med*, 1923, vi, 13-16
- 27 NEUBURGER, J Das konstitutionelle Moment der perniziösen Anämie, *Morbus Biermer und Carcinom*, *Med Klin*, 1927, xxiii, 1731-1732
- 28 PLUMMER, N S, and SIMPSON, C K A case of carcinoma of the stomach occurring in a patient with atrophic gastritis who had recovered from Addison's anemia, *Guy's Hosp Rep*, 1931, lxxxi, 407-417
- 29 SIMPSON, C K A case of Addison's anemia with subacute combined degeneration of the cord associated with carcinoma of the stomach, *Guy's Hosp Rep*, 1931, lxxxi, 392-406
- 30 WEINBERG, F Karzinom und perniziöse Anämie, *Ztschr f klin Med*, 1917-1918, lxxxv, 392-405
- 31 STRANDELL, B Cancer of the stomach and pernicious anemia, *Acta med Scandinav, Suppl*, 1931, xl, 89-96
- 32 LEVINE, S A, and LADD, W S A clinical study of one hundred and fifty consecutive cases with special reference to gastric anacidity, *Bull Johns Hopkins Hosp*, 1921, lxxiii, 254-266
- 33 PANTON, P N, MAITLAND-JONES, A G, and RIMDOCH, G Pernicious anemia, an analysis of 117 cases, *Lancet*, 1923, i, 274-279
- 34 ROHNER, F J Pernicious anemia a study of one hundred and twenty-seven cases, *Jr Iowa Med Soc*, 1922, xii, 216-221
- 35 EISEN, D The anemia of cancer of gastrointestinal tract based on a study of 187 cases, *Canadian Med Assoc Jr*, 1927, xvii, 307-313
- 36 VON HOFFMANN, quoted by NEUBURGER
- 37 CORNELL, B S Pernicious anemia, 1927, Duke University Press, Durham, North Carolina
- 38 DAVIDSON, L S P, and GULLAND, G L Pernicious anemia, 1930, C V Mosby Company, St Louis, Missouri
- 39 HURST, A F Essays and addresses on digestive and nervous diseases and on Addison's anemia and asthma, 1924, Paul B Hoeber, Inc, New York
- 40 UNGLEY, C C Stomach and pernicious anemia, *Newcastle Med Jr*, 1929, x, 14-39
- 41 BRODERS, A C The grading of carcinoma, *Minnesota Med*, 1925, viii, 726-730

RENAL INSUFFICIENCY FOLLOWING BLOOD TRANSFUSION—RECOVERY AFTER VENESECTION*

By HENRY T VONDELSTEN, M D , F A C P ,

and

SAMUEL A COSGROVE, M D , F A C S ,

Jersey City, New Jersey

IN 1931, Bordley¹ reviewed the literature and analyzed 17 cases of renal insufficiency following blood transfusions. Eleven of these 17 cases died and six recovered. No patient recovered who had received more than 540 c c of blood, none died who had received less than 350 c c of blood.

The present case is reported as unusual, in that recovery followed transfusion of 750 c c of blood, and that it seemed to depend on venesection, a measure not evidently used in previous cases reported.

CASE REPORTS

Mrs. B., aged 32, wife of a physician, was the mother of three children, and had had one spontaneous abortion, all her pregnancies had been free of toxic symptoms, save for moderate hyperemesis during one of them, her labors had all been normal.

Her previous medical and surgical history was negative except for appendicitis with appendectomy six years before the present illness.

Following her last parturition six months ago, she had complained constantly of general malaise, weakness and coldness of the body surface, and a loss of 20 pounds in weight, there was a moderate anemia of secondary type: hemoglobin 65 per cent, red blood cells 3,600,000, white blood cells 8000. The urinalysis was normal. No satisfactory explanation of the cause of her anemia had been found. Various methods of therapy had not improved her condition, and it was hoped transfusion might do so.

She was admitted to Christ Hospital for this purpose June 4, 1931.

Blood count on admission was: hemoglobin 70 per cent, Sahli, red blood cells 4,200,000, white blood cells 7000, polymorphonuclears 70 per cent, lymphocytes 30 per cent. The blood was designated a Type II Jansky by two different laboratories. Cross matching between the donor and the recipient showed no hemolysis or agglutination.

Operation. Transfusion was begun at about 1 00 p m, June 5, 1931. Seven hundred and fifty cubic centimeters of whole blood were given by the Unger method. During the operation, the patient made no complaint, subsequently, she stated that a headache developed towards the end of the transfusion.

A sharp febrile reaction occurred which reached its maximum (103° F) seven hours after transfusion and receded to normal in 18 hours. For the remainder of her stay in the hospital, the temperature was within normal limits.

During this period of reaction, severe occipital headache, and intense pains in the limbs and lumbo-sacral region occurred. She felt nauseated and vomited several

* Received for publication November 11, 1932

times The vomitus contained blood A small quantity of urine was voided but, unfortunately, its characteristics were not charted

June 6th The pains in the limbs and back are not so intense The occipital headache has not lessened Pain and tenderness are especially referred to both mastoid regions Movements of the head are resisted, the neck is slightly rigid Nausea continues and a greenish-brown fluid was vomited once during the day Urinary output for the twenty-four hours only 200 cubic centimeters It contained much blood

June 7th During the early morning hours, the patient twice vomited a large quantity of bloody fluid Pain in the mastoid regions is complained of constantly and bitterly Urinary output 150 cubic centimeters, albumin 4 plus, many red blood cells, many shadow cells. These findings were regarded as indicating a combination of hematuria and hemoglobinuria Blood count—hemoglobin 87 per cent Sahli, red blood cells 4,600,000, white blood cells 17,200, polymorphonuclears 92 per cent, lymphocytes 8 per cent.

June 8th The pains have somewhat diminished In the right hypochondriac region, the kidney is palpable, feels enlarged and is tender on pressure Urinary output 300 cubic centimeters with the same characteristics as the day before Blood pressure 115 millimeters of mercury systolic and 80 diastolic

Examination of the optic fundi revealed no blurring of the discs, exudates, or hemorrhages Both tympanic membranes were normal Blood chemistry—urea N 50 mg, creatinine 3.7 mg, uric acid 2.8 mg, sugar 90 mg

June 9th Except for occasional nausea, the patient spent a fairly comfortable day Urinary output, 250 cubic centimeters

June 10th Complains less of pain and nausea One thousand four hundred cubic centimeters of fluid were retained by mouth and rectum Voided 600 cubic centimeters Vomited 200 cubic centimeters of fluid, the vomitus contained no blood Blood chemistry—urea N 66.6 mg, creatinine 7.5 mg, uric acid 3.8 mg, sugar 100 mg Spent a fairly comfortable day

June 11th Occipital headache has increased in severity The neck is more rigid A fine petechial rash has appeared over the abdomen, back and arms Blood pressure 140 millimeters of mercury systolic and 80 diastolic

Blood chemistry—urea N 72 mg, creatinine 7.8 mg, CO_2 combining power 63.3 volumes per cent Fluid intake 1700 cubic centimeters, urinary output 550 cubic centimeters It contained no blood

June 12th Outstanding symptoms, occipital headache and rigidity of the neck Vision is impaired, complains of blurring and loss of sight Ophthalmoscopic examination is negative Reflexes are somewhat hyperactive Babinski and Kernig signs are absent Lumbar tap—10 cubic centimeters of spinal fluid withdrawn, no increased pressure, clear, cell count 2, sugar reduction 3 plus, globulin negative, smear and culture negative Electrocardiogram negative

At 11:30 p.m. the patient had a generalized convulsion lasting one minute Fluid intake for the day 1250 cubic centimeters, urinary output 950 cubic centimeters, no blood

June 13th At 1:00 a.m. the patient had a generalized convulsion, later vomited and complained of severe frontal headache and vertigo At 3:45 a.m. had another convulsion

From 5:45 a.m. until 7:45 a.m. had many convulsions with short intervals of coma Intravenous glucose, intravenous and intramuscular magnesium sulfate had been administered but with no marked benefit Her condition was deemed desperate and we decided to bleed her

Phlebotomy was performed and 450 cubic centimeters of blood withdrawn Five hundred cubic centimeters of normal saline were introduced into a vein after the venesection Blood chemistry of the phlebotomized blood—urea N 75 mg, creatinine 7.5 mg

Immediately after the venesection, convulsions ceased, consciousness returned shortly, and the general condition greatly improved. During the day she slept for long intervals and asked for nourishment. Diuresis increased to 2500 cubic centimeters.

Blood count after the venesection: hemoglobin 50 per cent Sahli, red blood cells 2,890,000, white blood cells 18,600, polymorphonuclears 92 per cent, lymphocytes 8 per cent.

June 14th. Patient feels comfortable, except for slight attacks of momentary nausea and blurring of vision. Diuresis has increased to 3000 cubic centimeters.

June 15th. Diuresis continues and subsequently urinary output was normal while the patient remained in the hospital.

June 19th. Blood chemistry—urea N 30 mg, creatinine 27 mg, uric acid 25 mg, sugar 120 mg.

June 25th. Blood chemistry—urea N 10 mg, creatinine 15 mg, uric acid 21 mg, sugar 90 mg. Urine sp gr 1.013, albumin, trace, very occasional red blood cells and white blood cells.

June 26th. Patient discharged from the hospital.

Subsequent History. About five months after leaving the hospital, she had an attack of pain in the right hypochondriac region. This was accompanied by nausea and headache. The right kidney was palpable and tender. Only 30 cubic centimeters of urine were voided in twenty-four hours. The sp gr of the urine was 1.020, faint trace of albumin, no casts.

During the next day, the symptoms promptly subsided with the excretion of a large amount of urine.

A pyelogram taken shortly after this attack revealed a slight kink in the right ureter.

COMMENT

This case conforms in its major clinical manifestations and course to the group of cases cited by Bordley. The presumption is that the reaction noted depended on blood incompatibility. The recipient had been repeatedly typed as a Group II Jansky before operation, and the donor conformed to the same type by tests before and after the transfusion. The bloods were cross-agglutinated before operation without evidence of hemolysis or agglutination, but it is certain that this reaction was not observed for as long as two hours, which was the length of time before Bordley's first case did show slight agglutination on retest. Herein probably lies the source of error. Unfortunately, cross-agglutination was not subsequently repeated in this case.

The recipient's history and previous clinical observation showed nothing to indicate preëxisting nephritis. The donor's urinalysis and blood chemistry were normal.

It is not believed that the reflex anuria noted some months later, possibly dependent on kinking of the ureter seen in the pyelogram, was related to the condition following transfusion. It was transient, not accompanied by any evidence of nephritis or uremia, but was manifested by localizing symptoms not present during the more severe illness.

Inasmuch, however, as in the cases previously described there was no observation of anatomical anomalies, there might be speculation as to whether the existence of such lesions may contribute in any degree to insufficiency of the kidney due to blood incompatibility.

SUMMARY

1 A patient was transfused with 750 cubic centimeters of whole blood for secondary anemia

2 An immediate reaction occurred as evidenced by the sharp rise in temperature accompanied by hematuria, hemoglobinuria and oliguria

3 A delayed reaction occurred which reached its peak on the ninth day. This reaction was characterized by severe uremic symptoms, headache, rigidity of the neck, convulsions and coma. Repeated blood chemistry examinations during this period showed marked urea-nitrogen and creatinine retention, clinical and chemical evidence of renal insufficiency

4 Venesection of 450 cubic centimeters of blood followed by the introduction of 500 cubic centimeters of normal salt solution intravenously, resulted in an immediate cessation of uremic symptoms

5 Venesection as a method of treatment in renal insufficiency following blood transfusions has not been suggested or employed in cases reported in the meager literature on this subject to which we have had access

6 The subsequent attack of reflex anuria brings up the question of a mechanical factor in the development of renal insufficiency following blood transfusion

REFERENCE

- 1 BORDLEY, J, III Reactions following transfusion of blood, with urinary suppression and uremia, Arch Int Med, 1931, xlvii, 288-315

VITAMIN THERAPY IN PULMONARY TUBERCULOSIS*

IV COMPARISON OF THE H-ION CONCENTRATION OF THE BLOOD IN TUBERCULOSIS WITH NORMALS ON THE SAME DIETARY

By PAUL D CRIMM, M D ,

and

HERMAN L WATSON, B A ,

Evansville, Indiana

IN STUDYING the effect of vitamin D upon the calcium equilibrium of the human body infected with tubercle bacilli, normal chemical relationships are prerequisite. A normal blood calcium and phosphorus is interwoven in the physico-chemical complex of a normal acid-base balance. One of the factors representing this balance is the H-ion concentration of the blood. That H-ion concentrations within normal limits exist during the clinical course of many diseases is obvious, otherwise they would present to us an accompanying state of acidosis or alkalosis. Although bio-chemical tests other than pH give us a wider range of analysis and interpretation, yet the pH test interpreted with its accompanying variables makes this analysis an added criterion.

METHOD

Electrometric methods for determining the pH of the blood plasma are too intricate and expensive for universal use. Several investigators have proved the accuracy of the glass electrode method for determining the H-ion concentration of the blood. Fosbinder and Schoonover¹ of the Cancer Research Laboratories under the direction of McDonald² made a comparative study of the glass electrode and colorimetric method of Hastings and Sendroy³. Hastings and Sendroy³ previously had improved Cullen's⁴ method. Fosbinder and Schoonover¹ found the average deviation between the two methods to be 0.002. McDonald's² modification of Hastings and Sendroy's³ method was used in making the following analyses of blood plasma.

EXPERIMENTAL REQUIREMENTS

Investigators in recent years are becoming more cognizant of the many physiological and chemical factors which might influence any analysis of the blood's constituents. For example, much previous work on serum calcium has been performed with disregard for calcium and phosphorus in the

* Received for publication November 11, 1932. From Boehne Tuberculosis Hospital, Evansville, Indiana.

dietary intake. Disregard of this one factor alone causes many interpretations to disagree. Whether the delicate pH test of the blood plasma will demand certain specific requirements in the diet for comparative analysis, is still a conjecture. At any rate, in this comparison, the normals and those patients infected with pulmonary tuberculosis, were on the same routine dietary. All analyses were performed during the months of May, June, and July. All determinations were performed by the same chemist. Bloods, for the most part, were drawn between the hours of 2 p m and 5 p m and examined immediately. This time of determination was considered satisfactory because the average of 22 determinations at 9 a m, 28 determinations at 2 p m and 34 determinations at 5 p m gave an average pH of 7.38 for each time group. This average does not represent a pH time element for a single day. Several patients had three determinations at 9 a m, 2 p m and 5 p m over a ten-day period and were also found to have an average pH of 7.38.

DATA

The following analyses were performed prior to the investigation of hypercalcemias. Table 1 lists the pH of 50 normal individuals. The average range of this normal group was 7.35 to 7.40. The average normal pH was 7.37. McDonald and co-workers² reported an average normal pH of 7.38 on 25 patients from November 1928 to January 1931. If we compute the probable error according to the formula $E = 67 \sqrt{\frac{\sum v^2}{n(n-1)}}$

TABLE I
List of Normal pH Values

No	Age	Sex	pH	No	Age	Sex	pH
1	24	M	7.38	27	23	F	7.38
2	23	M	7.39	28	19	F	7.39
3	48	F	7.36	29	23	M	7.39
4	27	F	7.39	30	43	M	7.37
5	21	F	7.38	31	18	F	7.38
6	45	F	7.40	32	21	F	7.36
7	36	F	7.36	33	25	F	7.37
8	22	F	7.38	34	46	M	7.38
9	45	F	7.39	35	56	M	7.39
10	22	F	7.38	36	22	F	7.37
11	21	F	7.37	37	58	M	7.37
12	47	F	7.38	38	29	F	7.39
13	19	F	7.39	39	23	F	7.38
14	35	F	7.37	40	24	F	7.37
15	21	F	7.39	41	27	F	7.37
16	40	M	7.40	42	19	F	7.39
17	22	F	7.39	43	19	F	7.36
18	19	M	7.37	44	18	F	7.37
19	18	F	7.36	45	23	F	7.38
20	23	F	7.37	46	18	F	7.40
21	24	F	7.38	47	18	F	7.38
22	59	M	7.37	48	24	F	7.36
23	35	M	7.35	49	26	F	7.38
24	52	M	7.36	50	29	F	7.37
25	25	F	7.38				
26	18	F	7.37				

Average = 7.37

for the group of pH normals, the coefficient of variation equals 001, which is well within the limits of experimental error According to Hastings and Sendroy³ this method permits the estimation of colorimetric pH values to within ± 02

Table 2 lists the pH of 75 patients in various stages of pulmonary tuberculosis The average pH range for these patients with pulmonary tuberculosis was 7 33 to 7 45, the average being 7 38 If we compute the probable error according to the formula $E = 67 \sqrt{\frac{\sum v^2}{n(n-1)}}$ for this group of pH determinations, the coefficient variation equals 0006, which is well within the limits of experimental error

TABLE II
List of pH Values in Pulmonary Tuberculosis

No	Age	Sex	Mean Temperature F	pH
STAGE I				
1	46	F	98 6	7 37
2	22	M	98 6	7 39
3	37	M	98 6	7 38
4	29	F	98 8	7 38
5	19	M	98 6	7 39
6	34	F	98 8	7 37
7	21	M	98 6	7 39
				Average = 7 38
STAGE II				
8	35	M	98 8	7 39
9	42	M	98 6	7 39
10	25	F	98 6	7 38
11	17	F	98 8	7 37
12	24	M	98 6	7 36
13	27	F	98 8	7 35
14	44	F	99 0	7 39
15	37	M	99 0	7 39
16	17	M	99 6	7 40
17	42	F	99 0	7 36
18	27	F	99 0	7 39
19	20	M	98 8	7 39
20	26	F	99 4	7 42
21	34	F	98 8	7 38
22	24	F	98 8	7 38
23	14	F	98 8	7 37
24	19	F	99 0	7 39
25	28	F	99 0	7 39
26	28	F	99 4	7 40
27	18	F	98 8	7 34
28	16	F	99 0	7 36
29	24	F	98 6	7 37
				Average = 7 38

TABLE II (Continued)
List of pH Values in Pulmonary Tuberculosis

No	Age	Sex	Mean Temperature F	pH
STAGE III				
30	24	F	99.6	7.38
31	27	F	99.2	7.38
32	25	M	99.0	7.37
33	28	M	98.8	7.39
34	35	F	98.8	7.39
35	27	M	99.0	7.38
36	39	M	99.6	7.33
37	17	F	100.6	7.42
38	45	M	98.6	7.38
39	17	M	98.8	7.38
40	20	F	99.4	7.37
41	54	M	99.6	7.36
42	30	F	99.2	7.43
43	14	F	101.0	7.42
44	31	F	99.2	7.37
45	33	M	99.0	7.37
46	39	F	99.0	7.40
47	41	F	99.6	7.37
48	38	F	99.0	7.45
49	41	F	99.2	7.36
50	22	F	100.0	7.37
51	19	M	99.0	7.37
52	55	M	98.6	7.39
53	27	M	99.2	7.35
54	54	M	100.0	7.42
55	28	M	98.0	7.34
56	35	F	99.6	7.35
57	17	M	99.0	7.39
58	14	M	99.6	7.43
59	29	F	101.0	7.45
60	40	F	99.4	7.42
61	18	F	99.0	7.37
62	55	F	99.6	7.44
63	45	M	99.0	7.42
64	44	M	99.6	7.39
65	48	M	99.4	7.39
66	28	M	99.4	7.37
67	48	M	100.0	7.43
68	30	M	100.0	7.40
69	30	F	99.6	7.40
70	22	F	99.6	7.39
71	27	F	99.4	7.39
72	61	M	99.2	7.42
73	26	M	98.6	7.39
74	26	F	99.8	7.39
75	35	F	99.2	7.41
				Average = 7.39
				Total Average = 7.38

COMMENT

Patients with pulmonary tuberculosis showed a slightly increased pH of the blood when compared with normal individuals. The group in Stage I is afebrile. The average pH for this group is 7.38. In the Stage II group, there were slight elevations of temperature. It so happened that

each patient that had a temperature of at least 99.4° also had a pH of 7.40 or more. The average pH for this group is 7.38. However, in the Stage III group, several patients with 99.4° had a pH under 7.40 but all the patients in this group except one, that had a temperature of 100° or more, had a pH ranging from 7.40 to 7.45. The average pH for this Stage III group is 7.39.

Other factors being equal, it is apparent that the febrile condition accompanying patients with pulmonary tuberculosis in Stage II, and particularly those in Stage III, was responsible for the slightly higher elevation of the pH. Kast, Myers and Schmitz⁵ found the pH somewhat higher than normal in febrile patients. Peters and Van Slyke⁶ in summarizing their work⁵ and that of others done on pH and CO_2 content of the serum in febrile patients say, "one cannot conclude with certainty that in the cases reported the cause of the observed effects on the acid-base balance was the fever rather than other influences of the diseases." The patients in this series who had a temperature of 100° or more had an average pH of 7.41. In our opinion the disease of pulmonary tuberculosis, other metabolic processes being normal, affects very little, if any, the H-ion concentration of the blood unless a febrile condition exists.

SUMMARY

The average normal pH performed on 50 normal individuals is 7.37. The average pH performed on 75 patients in various stages of pulmonary tuberculosis is 7.38.

It is also significant to note that a slightly wider range of pH existed in patients with pulmonary tuberculosis, namely a pH of 7.33 to 7.45 against the normal's range of 7.35 to 7.40.

It is apparent that the febrile condition accompanying patients with pulmonary tuberculosis is responsible for a slightly decreased H-ion concentration (pH increased).

BIBLIOGRAPHY

- 1 FOSBINDER, R. J., and SCHOONOVER, J. An improved method of measuring glass electrode potentials, *Jr Biol Chem*, 1930, **LXXXVIII**, 605.
- 2 WOODWARD, G. E., SCHOONOVER, J. W., FRY, E. G., TORRANCE, E. G., and McDONALD, E. The hydrogen-ion concentration of the blood in untreated cancer cases and its relation prognosis, *Jr Lab and Clin Med*, 1931, **xvi**, 704.
- 3 HASTINGS, A. B., and SENDROY, J., JR. Studies of acidosis. XX. The colorimetric determination of blood pH at body temperature without buffer standards, *Jr Biol Chem*, 1924, **lxi**.
- 4 CULLEN, G. E. Studies of acidosis. colorimetric determination of hydrogen-ion concentration of blood plasma, *Jr Biol Chem*, 1922, **lii**, 501.
- 5 KAST, L., MYERS, V. C., and SCHMITZ, H. W. Clinical conditions of alkalosis, *Jr Am Med Assoc*, 1924, **LXXII**, 1858.
- 6 PETERS, J. P., and VAN SLYKE, D. D. Quantitative clinical chemistry, Volume I, 1932, Williams and Wilkins Company, Baltimore.

THE CLINICAL VALUE OF THE PRESUMPTIVE KAHN TEST*

By TOMAS CAJIGAS, M S , M D , F A C P ,
Washington, D C

SOON AFTER the development of the standard Kahn reaction in 1923, Dr Kahn proposed a more sensitive method, which he named the Presumptive test, to be employed as a check on the standard method¹ Since that time the standard reaction has become an accepted method throughout the world The same cannot be said, however, in the case of the presumptive reaction One finds comparatively few reports in the literature on this reaction, indicating that it is relatively little used The reason for this may be the fact that serologists who often employ the Kahn with the Wassermann test have the feeling that two tests are sufficient Then again, some serologists prefer to resort to precipitation methods, such as the Kline or Meinicke tests, if they wish a check of the Wassermann and Kahn reactions

In our own laboratory, it has been our practice to use the Wassermann and Kahn tests routinely About three years ago, we added the presumptive Kahn to these two tests and we believe that we have increased the correctness of our serologic results during this period to an extent that more than compensates for the effort and expense in performing this test

Let us first consider the results with the presumptive Kahn test reported by other workers.

McDermott² in a study of 15,000 cases found the presumptive test to be 2 per cent more sensitive than the regular Kahn in the general run of hospital cases and 26 per cent more sensitive in treated cases of syphilis In a comparative study of 1300 spinal fluid Kahn tests, the same worker found the presumptive to be 12 per cent more sensitive than the standard Kahn in the general run of hospital cases and 18 per cent more sensitive in treated cases of neurosyphilis

In a clinical study of the standard and presumptive Kahn reactions in neurosyphilis made by Davenport,³ the standard reaction with spinal fluid was found to be highly specific for neurosyphilis, but it occasionally gave a negative reaction in the presence of this clinical condition Thus in 118 untreated cases of neurosyphilis, two negative standard Kahn reactions were obtained and in 369 treated cases of neurosyphilis, 23 negative standard Kahn reactions were obtained in patients who required further central nervous system therapy Turning to the presumptive procedure, however, of 115 positive reactions obtained in a group who have received no treatment for neurosyphilis, 13 were obtained in syphilitic patients who showed no clinical evidence of neurosyphilis In other words, all positive spinal

* Received for publication January 23, 1933

fluid reactions given by this method were cases of syphilis and it may indeed be that this test is the earliest indicator of neurosyphilis available today, giving positive reactions long before there are clinical manifestations of this condition. With regard to treated cases of neurosyphilis, Davenport reports 30 positive spinal fluid reactions on patients who clinically required no further therapy to the central nervous system, and four negative reactions on patients who, although apparently well and at work, were in need of further treatment as a factor of safety. In short, the presumptive spinal fluid test seemed to be far more sensitive than the standard Kahn test both in untreated and in treated cases of neurosyphilis.

Turning to the results of the presumptive test at the Montevideo conference,⁴ it might perhaps be well to first emphasize that this conference was competitive in nature to the same extent as the Copenhagen conference. Bloods were collected from known cases of syphilis and from non-syphilitic controls in various hospitals of Montevideo as well as in medical centers of Buenos Aires and Rio de Janeiro from where they were sent by air mail to the Prophylactic Institute of Montevideo where the conference was held. A total of 927 serums were examined. Of these, 623 came from cases of syphilis, including all stages, both treated and untreated. The remaining 304 came from non-syphilitic persons, most of whom, however, suffered from some pathological condition other than syphilis.

Table 1 was taken from the official report of the League of Nations' Health Committee of the Montevideo conference. It is evident from this

TABLE I

The Results Obtained by the Various Methods at the Montevideo Conference, Expressed on a Percentage Basis

(From League of Nations, Health Organization, Report of Montevideo Conference, Geneva, 1931)

Method	Percentage Syphilis	Positive Reactions
		Non-syphilitic Controls
		One per cent or less of non-specific reactions
Kahn's "presumptive" test	75.6	1.0
Muller's clotting test (M B R 11)	69.3	0.7
Kahn's "standard" test	63.9	0
Modified B-W test performed by Sordelli and Miravent	55.9	0
Modified B-W test performed by Wjler	54.4	0
Modified B-W test performed by Scaltritti and Cassiniga	49.9	0
		More than 1 per cent of non-specific reactions
Modified B-W test performed by Moreau	64.7	13.9
Meincke's clarification test (M K R.) performed by Dussert-Jelland	62.2	2.4
Modified B-W test performed by Torrazza and Lorenzo	55.5	2.6
Modified B-W test performed by de Assis	54.9	4.3
Sero-haemo-flocculation test performed by Prunell	52.4	4.5
Modified B-W test performed by Puppo	45.4	5.6

table that the presumptive test was more sensitive than the other methods employed, giving 75.6 per cent positive reactions while some methods in the same group of syphilitic cases gave as low as 45 to 50 per cent. With regard to positive reactions obtained in non-syphilitic cases, only four methods were free from such reactions: the Kahn standard reaction and three Wassermann methods; these three, however, were considerably less sensitive than the Kahn reaction. The remaining eight methods gave varying numbers of false positive reactions. The presumptive test gave 1 per cent, and the other seven methods gave from 0.7 to 13.9 per cent of such reactions. It is evident that the presumptive test, in spite of its high specificity, gave a relatively small number of false positives at that conference.

Table 2 presents in actual figures the increase in sensitivity of the presumptive over the other tests at the Montevideo conference. Of 623 treated

TABLE II

The Results of the Presumptive Kahn Test at the Montevideo Conference

Wherein this test was compared with 7 different Wassermann tests and 4 precipitation tests in the examination of 623 cases of syphilis (untreated and treated) and 304 non-syphilitic controls

Method	Performed by	No of Positive Reactions in Syphilitic Group	Increase in Sensitivity of Presumptive over Other Tests	No of Positive Reactions in Non-Syphilitic Group
Presumptive	Kahn (University of Michigan, Ann Arbor)	471		3
Standard Kahn	Kahn (University of Michigan, Ann Arbor)	398	18%	None
Wassermann	Sordelli (Nation Bact Inst, Buenos Aires)	347	36%	None
Wassermann	Harrison-Wyler (Ministry of Health, London)	339	39%	None
Wassermann	Scaltritti (Prophylactic Inst, Montevideo)	311	51%	None
Wassermann	Torrazza (Medical School, Montevideo)	346	36%	8
Wassermann	deAssis ("Vital Brazil" Inst Rio de Janeiro)	342	38%	13
Wassermann	Puppo (Sanit Military Service, Montevideo)	283	66%	17
Wassermann	Moreau (Medical School, Montevideo)	402	17%	42
Memicke MKR	Dussert (Nat'l Bact Inst, Santiago)	387	21%	7
Prunell	Prunell (Nat'l Health Dept, Montevideo)	330	44%	14
Muller MBR 11	Muller (General Hospital, Vienna)	432	9%	2
Average increase in sensitiveness of the Presumptive Test			34%	

and untreated syphilitic cases examined, the presumptive test gave 471 positives, while the number of positives given by the other methods varied from 283 to 432. When one considers the average increase in sensitiveness of the presumptive test over all of the other methods tested at Montevideo, one finds it to be 34 per cent.

We have adopted the practice in this laboratory, whenever confronted with negative standard Kahn and Wassermann tests and positive presumptive reactions, of routinely communicating with the clinician who submitted the specimen. In each instance where it was possible to obtain the correct history or when it was possible to study the patient more fully, it was ultimately established that the positive presumptive test was a specific reaction.

Table 3 gives the results of the presumptive test in comparison with the standard Kahn and Wassermann tests in 3,182 cases. Of this number

TABLE III

Increase in Sensitivity of Presumptive Kahn Test over the Standard Kahn and the Wassermann Tests in a Group of 3,182 Cases

No of Cases	Presumptive Kahn Test	Standard Kahn Test	Wassermann Test
498	+++, +++++	+++, +++++	+++, +++++
89	+++, +++++	++, +++++	+, ++
87	+++, +++++	+, ++	—
79*	+++, +++++	—	—
97*	+, ++	—	—
2332	—	—	—
Per cent Positive by all Methods			18.4
Per cent Negative by all Methods			73.3
Per cent Positive by Presumptive and Standard Kahn and Negative by Wassermann			2.7
Per cent Positive by Presumptive Kahn and Negative by Standard Kahn and Wassermann			5.5

* Of this group of 176 patients, 70.4 per cent (124 cases) represent patients under treatment, 7.4 per cent (13 cases) were diagnosed as syphilis—9 patients in this group were in the primary stage with positive dark-field findings, 22.1 per cent (39 cases) were undetermined, we having been unable to secure definite data as to the presence or absence of syphilis.

there was complete and relative agreement in 2,830 cases. Eighty-nine strongly positive presumptives gave moderately positive standard Kahn and weakly positive Wassermann tests. Eighty-seven strongly positive presumptives gave moderate and weakly positive standard Kahn tests with negative Wassermann tests. We are not concerned about this group of cases because of the well known specificity of the standard Kahn test. What concerns us especially is the group of 176 patients who gave positive presumptive tests and negative tests with the other two methods. Of these 176 patients, 124 (70.4 per cent) were under treatment for syphilis. 13 (7.4 per cent) were cases presenting themselves for diagnosis who had not as yet received treatment. Nine of these 13 cases were in the primary stage with positive dark-field findings. The remaining 39 cases (22.1 per cent) were undetermined, we having been unable to secure definite data as to the presence or absence of syphilis. Of the 97 cases listed in the table as one plus or two plus reactions, the vast majority were two plus reactions. From the facts presented in this table it is evident that the presumptive Kahn test detected significant reactions in 137 cases of syphilis during the past three

years that would not have been detected by the standard Kahn and Wassermann tests

There is some controversy today as to when treatment should be discontinued and there are some syphilologists who believe that it is not essential to treat the patient until all serological evidence of syphilis has disappeared. It has been most interesting to us in this study to notice that among the patients who continued to receive treatment for some weeks after the presumptive Kahn became completely negative, not one has shown any symptoms of syphilis or any serologic evidence of this disease, while those patients who have discontinued treatment while the presumptive reaction was still partly positive frequently on subsequent check up have shown definite positive reactions by all methods employed.

Before closing, I should like to quote the statement of a well known pathologist regarding the presumptive reaction. The late Dr. Aldred Scott Warthin who was a student of syphilis for thirty-five years, made the following statement in his lecture "The Problem of Latent Syphilis" before the Institute of Medicine of Chicago (November 21, 1930):⁵

The correlation between the tissue lesions and the serological reactions offers very definite problems. There was only about a 50 per cent agreement between the Wassermann reaction and the histologic findings in our cases. During the last two years the Kahn reaction has been used in our hospital with a much higher per cent of agreement. In the case of the presumptive Kahn, with a more sensitive antigen the agreement has reached about a 97 per cent degree. In several cases with a four plus presumptive Kahn, the clinicians have wholly denied the possibility of the patient having syphilis, when on autopsy a very active syphilitic aortitis was found. In our experience then, the Kahn test shows a much higher degree of accuracy when checked with the microscopic findings than does the Wassermann. We have had no false positives, and but few negatives.

CONCLUSIONS

- 1 The presumptive Kahn test is an extremely sensitive method for the detection of syphilis.
- 2 In 3182 examinations of blood the presumptive test was found to be more sensitive by 8.2 per cent than the Wassermann test and more sensitive by 5.5 per cent than the standard Kahn test.
- 3 The presumptive test appears to possess also a high degree of specificity and furnishes a valuable addition to the standard Kahn and Wassermann tests in the detection of syphilis.
- 4 The presumptive test is of value as a criterion in establishing the absence of syphilis. Due to the high sensitivity of the presumptive test, it is obvious that a negative reaction by this method has greater significance than a similar reaction given by less sensitive methods.
- 5 A great deal of valuable information may be gained by the use of the presumptive test as a check on other reactions for syphilis.
- 6 The presumptive test is of special value in primary syphilis, latent syphilis, neurosyphilis and in determining when to discontinue treatment.

REFERENCES

- 1 KAHN, R L Serum diagnosis of syphilis by precipitation, governing principles, procedure and clinical application of the Kahn precipitation test, 1925, Williams and Wilkins Company, Baltimore, Maryland—The Kahn test, a practical guide, 1928, Williams and Wilkins Company, Baltimore, Maryland
- 2 McDERMOTT, E B Presumptive Kahn procedure in syphilis based on 15,000 examinations, *Arch Path*, 1929, viii, 661–663—Kahn presumptive procedure with spinal fluids, *Arch Neurol and Psychiat*, 1930, xxiii, 531–535
- 3 DAVENPORT, K M Clinical value of Kahn test with spinal fluids, *Am Jr Syph*, 1929, xiii, 570–574—Clinical value of presumptive Kahn test with spinal fluids, *Am Jr Syph*, 1929, xiii, 575–582
- 4 Report of Laboratory Conference on Serodiagnosis of Syphilis convened at Montevideo, Geneva, League of Nations Health Organization, 1931
- 5 WARTHIN A S Eleventh Pasteur Lecture (November 21, 1930), Institute of Medicine, Chicago

THE SOURCE OF MODERN MEDICINE*

An Address to the American College of Physicians

By SIR ANDREW MACPHAIL, *Montreal, Canada*

Gentlemen I must trouble you with a date, 1685, the year in which Charles II died. That reign marks the watershed between the medieval and the modern world, between the mass and the individual, between authority and experience, between books and experiment. From that summit the spring of modern medicine burst forth.

It was in reality a new world. The Royal Society had been founded, the circulation of the blood had been proved, the Cartesian method had been disclosed, the universal law of gravity and the laws of planetary motion had just been announced. Logarithms, electricity, magnetism, chemistry were words coming into common use.

Up to that time, the authority in science was Aristotle, in philosophy, Thomas, in medicine, Galen. All three had organized and synthesized the existing knowledge of their day. It was a useful task, but when life is too closely organized it begins to perish. The body of knowledge then becomes a burden, a tradition, it blinds men's eyes, it makes them incapable of observation or thought. It enslaves them, but suddenly, freedom asserts itself. Freedom too has perils, but they are less dangerous than the perils of slavery. One can now say what he likes, even in medicine, no matter how foolish, there will be plenty to contradict him.

There were reasons deeper still for the scientific renaissance of the period under review. The divine right in science of Aristotle and the Greeks had passed, the divine right of kings in politics perished at the hand of Cromwell, the divine right of Galen in medicine came to an end with the appearance of Thomas Sydenham, and so we have come to our subject at last.

For a perfect sight of the old medicine, let me conduct you to the bedside of Charles II. With a cry he fell. Dr. King who, unfortunately, happened to be present bled him with a pocket-knife. Fourteen physicians were quickly in attendance. They bled him more thoroughly, they scarified and cupped him, they shaved and blistered his head, they gave him an emetic, a clyster, and two pills. During the next eight days they "threw in" 57 separate drugs and, towards the end, a cordial containing 40 more. This availing nothing they tried Goa stone, which was a calculus obtained from a species of Indian goat; and as a final remedy, the distillate of human skull. In the case report it is recorded, that the emetic and the purge worked so mightily well it was a wonder the patient died. One physician did protest that they would kill the king; and out of this arose the suspicion that he had

* Read before the American College of Physicians, Montreal, Canada February 8, 1933
From McGill University Montreal Canada

been irregularly poisoned. But he did die, "as peaceable as a lamb", his last words were, "Do not let poor Nellie starve"

While this medieval practice was in progress at the palace, not far away, on the north side of Pall Mall, looking south over St James' Park, opposite to Nelhe's, and quite near the house of Moll the dancer, lived Thomas Sydenham. But he was not called to the royal bedside. He was a Puritan, he had been a captain of horse in the parliamentary army, and, worse still, he was reputed to be practising medicine "in a new way". Out of his specifically creative mind modern medicine was already emerging by this new way.

His method was no secret. Twenty years ago, he had published his method of curing fevers, he was ready to publish his *Observations*, a series of five letters addressed to friends. "about the sum of all I know of the cure of disease up to the day on which I write, namely the 29th September, 1686". He died three years later. A collection of letters to his son was issued after his death. That is all. He lies buried in the church of St James', Piccadilly, where a mural tablet was put up by the Royal College of Physicians in 1810. It bears the inscription adapted from Horace, *Medicus in omne ævum nobilis*,—a physician famous for all time.

The most casual reading of his little books reveals the method. There is no dogma, no system, no body of doctrine, merely a few general principles. It is not a method even, it really indicates a way of looking at things, without searching too curiously into their causes. He looked upon diseases as they appeared to him, and made a complete study of each.

Most forms of disease, he thought, had a definite and uniform type due to the uniformity of the cause. He sought only for the "evident and conjunct causes", the remote ones he thought it vain to seek. Acute disease he considered to be a reaction of the body to meet some injurious influence coming from without. He was content to watch and aid in the natural crisis. Chronic diseases were in the main due to errors in diet and in the general way of life. As he put the case, "Acute disease is an act of God, of chronic disease the patient himself is the author."

Fever was nature's engine against the enemy, or her handmaid for removing the morbid material from the blood. Fever was a sign that nature was curing the disease, and should not be curbed unless it becomes too violent. The patient should be lightly covered, he should be allowed air and light, with water if he was thirsty, and food only when his appetite demanded it.

To do without hypotheses, and study the actual disease with an open mind, to make an unbiased study of the natural processes in health and disease, to trust in the healing power of nature—for nature is the mother and healer of us all—and provide help only when help was demanded—that was his re-discovery, for the original discovery had been made by Hippocrates himself.

He demanded that a physician should regard disease with the eye of a naturalist, and describe it with equal care. "If only one person in every

age," he said, "had accurately described and habitually cured only one single disease, and disclosed his method, physic would not now be where it is" Every hypothesis must be abandoned, while every phenomenon of disease is being minutely observed, "but it is right and necessary to distinguish between the constant characteristics of a disease and those that are merely accidental and adventitious. Want of accuracy in distinguishing diseases that are apparently similar is fatal to medicine"

Sydenham, of course, had his own theories, but he was never enslaved by them. Still less was he enslaved by classical dogma or by the chemical theories then in vogue. He made his own the great saying of his favorite, Bacon: "We have not to imagine or to think out, but to discover what nature does." These are the very words that Hunter addressed to Jenner, "Do not think—try."

In practice Sydenham did not disdain the use of drugs, he used Peruvian bark freely, as well as laudanum which he was the first to prepare, but he had many cases, "in which he consulted his patient's safety and his own reputation most effectually by doing nothing at all." It was a great mistake, he declared, to suppose that nature always needed the assistance of art. His friend, John Locke, the philosophical father of Hume and Kant, himself a captain in the army of the parliament, and a practising physician as well, in commending the new method writes to a friend, "You cannot imagine how far a little observation will carry a man in the curing of disease, though very stubborn and dangerous, and that with very little and common things, and almost no medicine at all."

Too much has been made of Sydenham's contribution to the diagnosis of disease. True, he distinguished between chorea and St. Vitus dance, he described syphilis, and recognized many diseases as specific in the modern sense, he established hysteria as a definite disease, his description of gout remains unexcelled. It was from that malady he suffered and died, but he consoled himself with the reflection, that fools rarely suffer from it, unless indeed he himself might have been an exception. He missed many of the symptoms of scarlatina, and his classification of fevers remains obscure.

It was in practice he excelled. For a patient who had suffered from the prevailing lowering treatment he prescribed a roast chicken and a pint of canary wine. A hypochondriac he advised to consult a physician in Inverness. The man proceeded on horseback, he could not find the doctor, he returned very angry but cured. "Nothing," Sydenham said, "so cherishes and strengthens the blood and spirits as riding a horse."

In addition to all this, there was in Sydenham, as there was in Hippocrates, in Pasteur, and in Lister, a powerful moral element which shines on every page. "Whoever," he wrote, "applies himself to medicine ought seriously to consider first, that he will one day have to render an account to the Supreme Judge of the lives of the sick committed to his care, and next, that whatever skill or knowledge he may, by divine favor, possess should be devoted above all else to the glory of God and the welfare of hu-

manity" And again, "the physician will care for the sick with more diligence and tenderness if he remembers that he himself is a fellow-sufferer"

Sydenham created no great stir in London To the end of his days he remained on the outside of the faculty, although he had his friends within and without, and in that Invisible College which was the precursor of the Royal Society To us who are alert for any new method the conduct of the profession towards Sydenham seems strange For thirty years he was described as a "sectary" In one of the few letters now extant, written in English, he admits that, "while he has the happiness of curing his patients, some of the faculty take fire at his attempts to reduce practice to a greater easiness" In another letter he utters a mild protest against those who make it a matter of reproach, if one brings forward anything new, which had not previously been said, or heard, by themselves

But the profession must not be too severely blamed We are so often right in our skepticism, we may be forgiven when we are occasionally wrong And Sydenham was quite "irregular" He practised in London until he was forty years old, without a license of any kind In 1663 he was admitted licentiate by examination of the Royal College of Physicians, which is the lowest rank It was not until 1676 that he acquired the doctor's degree, not from Oxford but from Cambridge He was at the time 52 years old, and his son was an undergraduate there He is known to have had the degree of bachelor of medicine from Oxford, but there is no official record In any case, his medical study must have been short, and not profound To compensate, he is alleged to have taken a postgraduate course at Montpellier There is no evidence of that either, although French writers make the most of the legend through the natural desire to claim him as their own

Even his unlicensed practice was interrupted by an excursion into politics in 1658, when he became a candidate for parliament He was unsuccessful, but as a defeated candidate he was appointed Comptroller of the Pipe, an office long since obsolete, and having to do with crown lands More important, he was awarded 600 pounds on account of his military service With this money in hand he married, and settled down to practise medicine

Likewise, his study preliminary to medicine was brief He entered Oxford at the age of eighteen, but after three months his career was interrupted by the outbreak of civil war He joined the army in company with three of his brothers, he kept the field for four years, when he returned to the University, and received an academic degree in 1646 Two years later, after his return from the second civil war, he was made Bachelor of Medicine by "actual creation" It was an honorary degree given in advance of the study for a profession which he entered by the influence of "a great man and by his own destiny"

It was quite natural, therefore, that he should be considered in London as an uneducated and unqualified person He could not write Latin, although he could read it, his writings must be translated for him, and the work was badly done Only rough notes in his own English remain, and it

is without especial quality. Although his pre-medical education was deplorable, he was not an ignorant man. He could speak Latin. Cicero was the author he most admired, "the great teacher both in thought and language." He frequently quotes Homer, Theocritus, Virgil, Horace, Juvenal, Seneca, and all modern Latin writers were known to him, especially Bacon and Erasmus. He knew the English Bible which was then a new book.

It was from Edinburgh and Leyden the fame of Sydenham first extended to the world. Boerhaave described him as the light of England, an Apollo in the art of medicine, a true pattern of the Hippocratic physician. Haller, a pupil of Boerhaave, who carried Sydenham's method to Germany, discovered him as the beginning of a new epoch in medicine. Van Swieten, a fellow-pupil, bore the seed to Vienna, where it developed into a great clinical school. Arbuthnot in the Harveian oration for 1727, found in him the "aemulus" or emulator of Hippocrates, and more recently the beloved Dr John Brown describes him as the prince of practical physicians.

This Boerhaave was professor of medicine in Leyden where he succeeded "Sylvius," who had made a vain attempt to reconstruct medicine upon a basis of the new chemistry and the circulation of the blood, losing himself in the technical and the mechanical. Boerhaave lectured five hours a day, his hospital contained only twelve beds, but by Sydenham's method he made of it the medical center of Europe. That knowledge came to him through Edinburgh from Archibald Pitcairne, who for a short time occupied the professor's chair in Leyden, and was the teacher of Boerhaave.

This Archibald Pitcairne was born in Edinburgh in 1652. His ancestor fell at Flodden with his seven sons. The family was continued by a posthumous child. He entered Edinburgh University in 1668, where he graduated Master of Arts in 1671, at the age of nineteen. Then he studied divinity and law. In Paris, where he went for his health, he began the study of medicine but soon returned to Edinburgh, and took up the study of mathematics and medicine. Once more he went to Paris, and graduated doctor of medicine at Rheims. He practised in Edinburgh with wide success, and in 1692 he went to Leyden to occupy a professor's chair. Two of his pupils were Boerhaave and Meade. In 1693 he returned to Edinburgh for his marriage to the daughter of an eminent physician, Sir Archibald Stevenson, from which place he often went as consultant to England and Holland.

Lacking the means of anatomical study, he persuaded the town council to permit him and some of his medical friends to dissect the bodies of paupers in Paul's Work, unclaimed by their relatives. The persuasion was easy, as they agreed to bury the bodies after dissection at their own charge, and to save the town from that expense. To this was added the somewhat dangerous provision, that they were to attend the patients free of cost to the town until they died. This was the origin of the Edinburgh school of medicine.

Anatomy has been the origin of every school of medicine. Human dis-

section is even yet the sovereign method of transforming the average layman into a physician. To this rule neither Hippocrates nor Sydenham is an exception. They did not dissect, but they were men of genius, and genius knows no law. Besides, they did not found schools. The fame of every school, McGill included, is based upon anatomy. It was fixed by Shepherd. I pause to utter a word of respect to his memory. In the modern sense he was not a teacher, but he compelled men to learn by the sheer drudgery of dissection,—dissection not of earthworms, frogs, rats or guinea-pigs, but of the human body. To him the human body, living or dead, was the primary unit in medicine, and in those days the ward-bed and the dissecting table were not very far apart. Indeed, as Sir John Bland-Sutton reminds us, the word *κλινη*, from which "clinical" is derived, applies equally to a bed and to a table.

I am well aware that in these days, when a student must be converted into a physiologist, a physicist, a chemist, a biologist, a pharmacologist, and an electrician, there is no time to make a physician of him. That consummation can come only after he has gone out into the world of sickness and suffering, unless indeed his mind is so bemused, his instincts so dulled, his sympathy blunted by the long process of education in those sciences, that he is forever excluded from the art of medicine which was to Hippocrates "the art" of all arts. In that case he is destined for the laboratory, the professor's chair, or the consultant's office. What would have happened to Sydenham, had he been put through this machinery is a problem in infinity which no human intelligence is competent to solve.

Pitcairne like Sydenham insisted upon the strictly scientific method long since enunciated by Bacon—an exact compliance with observation and experience. "Nothing," he affirms, "more hinders physic from being improved than the curiosity of searching into the virtues of medicine, but to enquire whence they have that power is a superfluous amusement, since nature lies concealed. A physician ought therefore to apply himself to discover by experience the effects of medicines and diseases, and not needlessly fatigue himself by enquiring into their causes which are neither possible nor necessary to be known." This is going too far, but we must agree that undergraduates in medicine and practitioners should be debarred from this "superfluous amusement."

Both Sydenham and Pitcairne were convinced that nature lies concealed, and always will be concealed. The more we seek the further she recedes. To pluck out the heart of her infinite mystery was to them a vain task and the seeker was sure to go astray. Nature knows no law. The laws of nature were merely our own presuppositions.

Pitcairne was also a poet, a mathematician, a scholar, a collector of books. His library was acquired by Peter the Great of Russia. His monument in Greyfriars churchyard bears an epitaph in testimony of his generosity to scholars. He was the first champion of Harvey. He too failed to win the approval of his colleagues, his plan for dissection was strongly opposed.

His way of life was equally disapproved by the Calvinistic Edinburgh. If we can believe his detractors, he was a frequenter of clubs, public-houses, and taverns. He is reputed to have been drunk twice a day, an unbeliever, much given to profane jests, an atheist, involved in quarrels with the faculty, and suspected by the government.

A curious evidence of his quality is supplied by Richard Meade, his pupil along with Boerhaave at Leyden, afterwards court physician to George II, better known as the discoverer of the *sarcoptes scabiei*, the insect that causes the itch. Pitcairne's son was out in 1715, and was condemned to death. Meade in gratitude to his master interposed and saved his life. He pleaded with Sir Robert Walpole, that if he and the royal family had been cured by his skill, it was due to the instruction he had received from Pitcairne.

The intermediary between Pitcairne and Sydenham was Dr Andrew Brown. He had read Sydenham's "new and quite contrary method." It so impressed him that he went to London "to settle his tossed thoughts." He spent "some months in his society," and found in him "everything that use to beget in wary and prudent people trust and knowledge." He returned to Edinburgh "as much overjoyed as if he had gained a treasure." He had, he published it to the world in 1691, "a vindictory schedule concerning the new cure of fevers, first invented by the sagacious Dr Thomas Sydenham." Pitcairne in the following year carried that treasure to Leyden.

Modern medicine had a resting stage in Edinburgh, whence it issued in two faint streams across the Atlantic to Montreal and Philadelphia. In 1821 the Montreal General Hospital was founded, and from it emanated the McGill medical school. This was the first hospital in America to introduce students into the wards. Here again the old and the new came into conflict. A duel was fought, men had conviction in those days. Five shots were exchanged with ounce bullets. One protagonist was shot through the chest, the other had his right arm shattered. Both recovered, the one by the old treatment, the other by the new, so their comparative merit was left undecided. The four founders were Edinburgh men.

When the College of Physicians of Philadelphia was founded in 1787, four of the eleven senior fellows had graduated from Edinburgh, and four others had studied there, "children of Edinburgh and grandchildren of Leyden" as Weir Mitchell said. There is in the Frick library a collection of 126 theses, presented by Sir William Osler, written by American students in Edinburgh between the years 1760 and 1813. Some of them bear the names of Morgan who founded the first American medical school in the University of Pennsylvania in 1763, of Shippen, Kuhn, Logan, Rush, and Lee. The first clinical lecture was given by Thomas Bond in 1766, on the advantages of clinical instruction. He took the precaution of reading it in advance to the board of managers who inscribed it in their minutes. To complete the record, Osler in 1885 went to Philadelphia, bearing with him what he had learned at McGill; and so these two streams of modern medicine were joined.

If I stopped at this point, I should be a mere historian repeating what you already know, or can read in books. Sydenham's little writings are at your hand in Latin and English, published by the old Sydenham Society. Everything germane to the subject has been collected by Dr F. Picard, and by J. F. Payne in 1900. From this material, small though complete as it is, many charming essays have been drawn, none more charming than that by H. H. Bashford in his Harley Street Calendar.

But history is the master to whom we all must go. If now we are convinced that Sydenham has achieved a world mastery in medicine we might do well to enquire how close we come to his mind, or how far we have departed from it. For the moment I shall content myself with one aspect—medical education—a subject upon which Sydenham expressed himself without reserve. We must not rely too implicitly upon even his authority for he had no experience in the public teaching of students, he never had a hospital appointment, never occupied a professor's chair. He had, however, some private pupils, one of whom was Dr. Dover whose powder yet bears his name. His own instruction at Oxford was scanty, he never entered a laboratory, never walked through a ward, there were no wards to walk in. He mentions Aristotle only once, Galen three times, Celsus not at all.

If a young man were to ask you by what means he should achieve a medical education, you would feel compelled to offer him the curriculum for the first two years. They are much the same, they represent the sum of our wisdom. In one recently under my hand, the first year is assigned to physiology, anatomy, histology, and organogen, although if the aspirant asked me what "organogen" meant, I should be obliged to confess that I do not know, unless indeed it is derived from the Greek word *ὄργανος* through the Latin *organer*. In the second year, biochemistry and pharmacology are added, with lectures on public health and the history of medicine. It is not on record that the neophyte comes into the remotest contact with a sick human being for two years. The London schools are within the hospitals and students from curiosity or boredom wander with new interest and profit into the wards. The French go to the other extreme, and assign clinical duties to a student on the first day of his entrance.

This very question of medical education was put to Sydenham by Hans Sloane, who afterwards achieved the highest professional and social honors, and is yet remembered as the founder of the British Museum. The young man modestly suggested that he might take a course in anatomy and botany. "This is all very fine," said Sydenham, "but it won't do. Anatomy, botany,—Nonsense Sir. I know an old woman in Covent Garden who understands botany better, and as for anatomy, my butcher can dissect a joint full as well. No, young man, all this is stuff you must go to the bedside, it is there alone you can learn disease." Rather than go abroad to study botany, he recommended this earnest seeker to drown him-

self in a pond that was commonly used for that purpose. The frightful thing is that he may have been right.

Sydenham was a physician, an artist, a practitioner; he thought that enough for any one person. He was not an ultimate scientist, not a botanist, anatomist, or physiologist. These were separate trades, they concerned him indirectly or not at all, they destroyed in the practiser the quality of physician. He had a passion for curing the sick, which expelled all other interests.

He does not seem to have heard of Harvey or the circulation of the blood, which was then a discovery 40 years old. Osler goes further when he writes: "There was nothing in Harvey's discovery which could be converted immediately into practical benefit, nothing that even the Sydenham of his day could take hold of and use." He knew nothing of Malpighi's discovery of the arterioles twenty years earlier. Indeed he averred that not even the microscope could disclose them. These to him were explanations, and he kept his mind upon the majesty of open facts. He gave to medicine a method which was more valuable than detailed discovery, he brought canonical authority to an end. But, strange to say, this method was soon to be extended into those fields of science of which he professed himself negligent or ignorant. Boerhaave applied that method to anatomy, physiology, and the microscope. Haller bore it with him to Gottingen, and developed physiology into a natural science, Morgagni in morbid anatomy was "the counterpart of Sydenham."

If Sydenham in his mature age began to practise in any American city, he would be put in gaol, if he applied with his poor preliminary qualification to study medicine in the first year of any medical school, he would be put in the asylum, along with Shakespeare, if he were found wandering about, after he had applied to a high-school as an instructor in English composition. We in Canada have been in the habit of blaming the United States for our established curricula. Forty per cent of our medical students at McGill are Americans, they help to pay our salaries, although they do profit to the extent of 600 dollars a year from our pious endowments.

In times gone by, Canadian graduates went freely to the United States to practise. We felt obliged to conform with the regulations of the various State boards, we still feel obliged in a measure to meet the legal needs of our American students. Now the border is more strictly closed. If an American physician comes to us, he comes on his own record since graduation. No one thinks of asking how or where Penfield, or Cone, or Stehle studied. If now our curricula are too abstract, the fault is our own. We have to deal only with the various provincial boards. The eye of the legislatures is upon them and upon us, and they are swift to act. One Canadian provincial board is much more rigid than any similar body in the United States. The final Report of the Commission on Medical Education, issued last month, discloses that all State regulations are completely relaxed, and the schools are now free. The head of one Board writes, that licensing

examinations, "as such," that is, apart from the candidate's school record, are worthless. Sydenham would sanction the profound sanity of this Report.

Let us now, in conclusion, try to discover if Sydenham's practice has any lesson for us. When he came upon the scene, practice had become so scientific that the most scientific physician did not even look upon his patients. In Paris their excretion was carried to him in an earthen vessel by a servant. By inspection of that alone he made a diagnosis, and sent the proper remedy. To be "elaborately curled" was a favorable sign. A similar practice prevailed in Scotland, if we can believe the panegyric of Robert Burns upon Doctor Hornbook, except that the mode of conveyance was upon a "kail-blade," that is, a cabbage leaf.

We in our time have departed still further from reality, when we substitute a photograph for the thing itself. The older surgeons were content to diagnose a broken leg if the end of the bone protruded through the skin. Now, we must have a picture. The fault is not wholly with the surgeon. The poorest patient is so hedged about with insurance that the surgeon must provide himself with the evidence the court may require. Nothing lies like the camera, especially when the deeper structures are involved. By a judicious use of the camera, a fish may be made to appear as long as the man who caught it. In hospitals, given over mainly to chronic and convalescent cases, an expert photographer comes once a week to "read" the pictures that have been made in the interval by the "technicians." He makes the diagnosis and suggests the treatment, although he has never seen a patient *qua* patient since the day he acquired his degree.

If Sydenham were alive today, and came into a modern hospital, he would be for the moment bewildered. He would have to teach himself that the field of medicine has been immensely widened, and cannot even be surveyed by a single mind. He would see acute conditions diagnosed at a glance, and swift treatment applied. But he would see obscure cases which had baffled practitioners as earnest as himself. He would discover, to his joy, that the chief physician was so scientifically conscientious that he would not make a diagnosis, still less prescribe anything more than a palliative treatment until he had before him all the reports of his various expert assistants. By the time the file was complete, the patient might have left the hospital alive or dead. If living, he might take his file with him, to display with the interest he had in his family album. But the visitor would recognize in that physician a brother to himself,—with this reserve, that the patient be not lost in the problem, or the physician in the abstract scientist. The world may be a stage; it is not a hospital, as the young man will discover when he begins to practise, deprived of apparatus, and compelled to rely upon his own natural senses.

Sydenham would be astonished at the magnificence of the modern hospital, and wonder if practice could not be reduced to a "greater easiness," thinking of the days when he fought his troopers and doctored them,

too, as indeed the soldiers in the recent war were adequately treated in aid-post, dressing station, field ambulance, and in rest stations for their convalescence. He would ask, as many are now asking, who bears the expense of three dollars a day for each public patient, described in his time as a pauper.

Unless the hospitals for public patients curb their scientific curiosity and return to the simple practice of Sydenham, their task will be taken away from them and given to another. Science, too, is governed by economic law. Even private patients are beginning to discover, as Sydenham did, that they can get well without becoming victims of the scientific ritual. Any patient who lives long enough will get well. Life is not now so desirable as it used to be. To die in peace is better than a few months of added misery.

Nature may be expelled, insensibly she returns. Happily, the tide of practice is now turning again to the bedside. The voice of Sydenham is being heard anew. To a patient clamoring for drugs and operation David MacKenzie said "The quickest and cheapest way to recovery is lying in that bed." Sydenham said to Locke "You will best cherish yourself by keeping to bed, it will contribute more to your relief than can be imagined." Dean Martin instructs his students that the educated hand and ear will tell the average physician enough, and all he can understand, towards treating a patient with heart disease. Electrical machinery is for the expert, he alone can tell if the fibrillations that appear upon the photograph are really in the heart or are due to extra-cardial electrical currents induced by a nearby radio or a vacuum cleaner in the hands of a ward-maid. John Meakins informs his students that the one question that really interests a patient is how soon he can resume his usual employment. Francis W. Peabody, six years ago, expounded to the students of Harvard the complete care of the patient.

Sydenham was a Puritan, he believed that scientific truth came as a revelation from heaven, or as we would say by an act of intuition in a creative mind. Experiments were of no avail, unless there was a mind to interpret them and discern the end to which they led. All else was mere research, searching for the already seen, or an aimless wandering in the mazes of nature. He made no objection to these experimenters. They might be as abstract and finical as they liked, he merely insisted that they know what they were trying to do, and above all keep out of the field of practical medicine, and not lead the minds of the young away from the bedside. There is a lesson in that for the laboratories.

Fame enough has come to Sydenham, but he had "long since weighed in a nice and scrupulous balance, whether it were better to serve men or be praised by them."

EDITORIALS

THE HEART AND THE SURGEON

IT SHOULD be of particular interest to physicians that some of the most important progress in the treatment of heart disease lies in the realm of surgery. It is very necessary for the physician to know what the surgeon can do and when to call him in.

Three totally different types of surgical procedure, each designed to relieve the sufferer from heart disease by altering certain of his physiologic processes, may be mentioned.

In the first place we have the nerve blocking procedures for painful afflictions such as angina pectoris. These, whether they be alcohol block, nerve section, or ganglionectomy, all serve merely to abolish pain by interrupting the arc over which the pain is referred. They cannot materially prolong life nor stay the progress of disease. Conceivably they may shorten life by removing the danger signal which pain may provide. However, because their use is commonly restricted to those patients whose misery is so great that life is not worth living this theoretical objection is of no moment. Since Jonnesco¹ first introduced procedures of this sort in 1916 much knowledge of the exact nature of the pathways has been gained with the result that the attack now should be made no longer upon the upper and middle cervical sympathetic ganglia, but instead upon the inferior cervical and upper dorsal ganglia or the posterior roots of the upper dorsal spinal nerves.²

Another category of cardiac operation is that of decortication or decompression of the heart. A pump enclosed in a rigid sack which does not permit it fully to relax obviously is handicapped in the quantity of pumping it can do. The heart may fall into this predicament when the pericardium is diseased as in constricting mediastino-pericarditis, of which the syndrome of Pick is an advanced stage. Also dense adhesions may so firmly anchor the heart to the unyielding chest wall that its action is grossly disturbed. In this event it may be more its contraction than its filling which is hindered. In either case the surgeon may be able to set free the struggling organ from restraint³ and relieve the patient of the symptoms that interference with heart action produced. The syndrome of Pick has been produced by the injection into the pericardial sack of substances which induce an adhesive process. This experimental syndrome has then been relieved by decortication of the heart.⁴ In somewhat similar fashion very huge hearts may

¹ JONNESCO, T. Traitement chirurgical de l'angine de poitrine par la resection du sympathique cervico-thoracique, Bull Acad de Médecine, Paris, 1920, LXXXIV, 93.

² WHITE, J. C., GARREY, W. E., and ATKINS, J. A. Cardiac innervation, experimental and clinical studies, Arch of Surg, 1933, XLVI, 765.

³ CHURCHILL, E. D. Decortication of the heart (Delorme) for adhesive pericarditis, Arch of Surg, 1929, LX (Part II), 1457-1469.

⁴ BECK, C. S. and GRISWOLD, R. A. Pericardiectomy in the treatment of the Pick syndrome, Arch of Surg, 1930, LXI, 1064.

suffer embarrassment from the very fact that the thorax itself becomes relatively confining. In such cases the substitution of a flexible for a rigid precordium through rib resection (decompression) may give greater ease of function.⁵

Endocardial operations have been tried, chiefly to relieve stenoses. They have not given results which are at all encouraging. Moreover while nerve block and decortication have in certain instances been brilliantly successful the cases in which they are indicated are far from plentiful. However, there is a totally different type of operation for heart disease which has been introduced quite recently by Blumgart and his collaborators,⁶ which bids fair to have a far wider application. This, like the other type, is based upon simple physiological principles.

The heart which is overburdened may be helped if its burden is reduced. The insufficiency of any organ may result on the one hand from an excessive demand placed upon it by the body as a whole, or on the other by a reduction in capacity for work of the organ itself. The two may be combined. The efficiency of organs in general depends upon the relation of *demand* for function and *supply* of function. The work performed by the heart is a function of mass of blood moved and resistance encountered. Mass of blood moved depends, primarily, upon the call for oxygen by the tissues, that is to say, upon metabolism.

The Boston investigators argued that reduction in metabolic rate by thyroidectomy ought to help certain cardiac cripples by reducing the work their hearts were called upon to do. If the heart's capacity cannot be increased the patients still may be benefited by making their hearts work less. At the lower level the heart may actually become competent. So they argued and since they had the courage of their convictions, so they carried on. In eleven of thirteen cases the results in the first few months seem brilliantly successful.

Of course it has long been known that the thyrocardiac is benefited by partial thyroidectomy. In the thyrotoxic person partial thyroidectomy usually permanently lowers metabolic rate. This is not so in persons with normal thyroid glands. In them the whole thyroid must be removed. If any gland tissue is left it soon hypertrophies and no permanent drop in metabolic rate is secured. The development of a safe technic for absolutely total extirpation of the normal thyroid gland is the contribution of Dr.

⁵ MORISON, A. Thoracostomy in heart disease, *Lancet*, 1908, 38.

LEFVORMANT, CH., and D'AUBIGNE, R. M. La thoracectomie precordiale dans les symphyes et certaines hypertrophies cardiaques, *J de chir*, 1928, xxxi, 161-175.

⁶ BLUMGART, H. L., LEVINE, S. A., and BERLIN, D. D. The therapeutic effect of thyroidectomy on congestive heart failure and angina pectoris in patients with no clinical or pathological evidence of thyroid toxicity, *Arch Int Med*, 1933.

BLUMGART, H. L., RISFMAN, J. E. F., DAVIS, D., and BERLIN, D. D. The therapeutic effect of total ablation of the thyroid on congestive heart failure and angina pectoris in patients with no clinical or pathological evidence of thyroid toxicity. III. Early results in various types of cardiovascular disease and coincident pathological states, *Arch Int Med* (In Press).

Berlin, the surgeon of the Boston group⁷ It is a very special technic, with considerable risk, a very different business from ordinary subtotal thyroidectomy for goiter It should be undertaken only by surgeons who have given it special study, by such, however, it may be successfully carried out The myxedema which will soon result in cases so treated can be perfectly controlled Patients with full-blown, spontaneous myxedema usually have metabolic rates of —40 or below They seldom show much clinical evidence of myxedema when their rates are not lower than —25 By the use of small doses of thyroid it will be quite easy to run these thyroidectomized cardiac patients at metabolic rates in the neighborhood of —25 which will avoid gross myxedema, yet effect a great saving to the heart

Another aspect of the matter is that of coronary flow The principle of demand and supply may be applied to coronary flow no less than to total cardiac work It has long been a common clinical experience to find that certain patients with myxedema develop angina pectoris when given thyroid Angina may be taken to be the symptom of relative insufficiency of coronary flow The myxedema patient's coronaries may be sufficiently capacious for his low rate of blood flow and consequent light cardiac work When his general metabolism and his heart metabolism are stepped up by the thyroid he receives, then his coronaries may become unable to meet their task Blumgart and his collaborators, recognizing this, argued that total thyroidectomy in ordinary cases of angina pectoris might, by lowering metabolic rate and diminishing the quantity of blood the coronaries are required to let pass, bring about a state of relative coronary competence Again in actual experience their thought seems to have been proved sound Indeed, it seems likely that total thyroidectomy may turn out to be a far better procedure for angina pectoris than any form of interruption of the nervous arc It may not only prevent pain but also prolong life

Progress of this kind indicates the necessity for a broadly physiologic point of view In the field of cardio-vascular disease the hemodynamic aspects must not be lost from sight in the welter of a mass of electrocardiographic and statistical facts What we want to know chiefly about a pump is how well it can pump, and the patient is keener to have us do something which will prolong and improve the pumping of his heart than he is to have us tell him with some nice degree of accuracy when it will cease

J H MEANS

SYPHILITIC AORTITIS

AMONG the lesions of late syphilis, syphilitic aortitis by virtue of its serious complications ranks high as a cause of fatalities It is estimated that cases of cardiovascular syphilis constitute over one-tenth of all cases of organic heart disease Moore believes that there may be as many as

⁷ BERLIN, D D The therapeutic effect of complete thyroidectomy on congestive heart failure and angina pectoris in patients with no clinical or pathological evidence of thyroid toxicity II Operative technic, *Am Tr Surg* (In press)

20,000 deaths a year from this cause in the United States. Of these a certain proportion are due to aneurysm, but the majority result from heart failure. For the most part it is not the aortitis which causes heart failure but the extension of the aortitis to the aortic valves with resultant aortic insufficiency, or the encroachment of the aortic lesions upon the openings of the coronaries bringing about stenosis or occlusion of these orifices.

It is still a subject of discussion whether a true syphilitic myocarditis occurs in association with specific aortitis or whether the pathological changes in the myocardium are explainable as a result of the mechanical stresses of the valvular lesion, the ischemia due to coronary stenosis at the ostia, or in many instances to the presence in the same patient of coronary arteriosclerosis. The inability of most pathologists to demonstrate spirochetes in the heart weighs somewhat against the specific nature of the lesions. In any case there is little evidence that a diffuse syphilitic myocarditis ever occurs in the absence of specific aortitis so that aortitis in nearly all cases may safely be assumed to constitute the primary syphilitic focus from which all lesions which cause heart failure later develop.

In the reports based on cases in which, irrespective of the cause of death, autopsy has demonstrated the presence of late syphilis it is shown that syphilitic aortitis is the commonest tertiary lesion with an incidence of approximately 80 per cent. In living patients, however, in whom the diagnosis of late syphilis has been made according to clinical and laboratory criteria, syphilitic aortitis is much less frequently diagnosed. In the analysis of a group of 6,420 ambulatory cases of late syphilis, Turner found evidence of cardiovascular syphilis in only 10.1 per cent, the diagnosis of uncomplicated aortitis was made in 5.1 per cent.

It is apparent that in known syphilitics the presence of syphilitic aortitis is frequently overlooked by our present methods of diagnosis and that moreover we are not able to utilize to the fullest the presence of this lesion as a means of diagnosing syphilis in cases presenting no other stigmata of this disease.

The diagnosis of syphilitic aortitis today is most accurate at a stage of the disease when the making of this diagnosis is least useful to the patient. When aneurysm, aortic insufficiency or symptoms of coronary stenosis are found we are frequently able to conclude that there is present an underlying aortic syphilis; but the opportunity for effective treatment in such cases has already passed. Treatment at best will only delay the inevitable end. To the individual patient at this stage, judicious treatment has much to offer, but no successful attack upon the mortality rate from cardiovascular syphilis can be initiated so late.

The diagnosis of uncomplicated syphilitic aortitis may be made with some certainty in a rather limited number of cases. In cases of known syphilis in which the ascending portion and the arch of the aorta are dilated, without other known cause such as hypertension and arteriosclerosis, the diagnosis of syphilitic aortitis is justified. The physical signs which sug-

gest such a dilatation, increased retromanubrial dulness, abnormal pulsation in the jugular fossa, drum-like aortic second sound are unfortunately easily overlooked perhaps because in some cases their significance is not appreciated and special attention is not given to their detection. Roentgenology may be of great assistance but here again routine procedures will often fail where more careful fluoroscopy from various angles or the use of oblique teleroentgenography would elicit evidence of dilatation.

A higher "index of suspicion" among physicians and consequent increased clinical alertness would no doubt add appreciably to the number of cases in which the diagnosis of uncomplicated syphilitic aortitis was arrived at by the determination of the presence of aortic dilatation. At best, however, this method of diagnosis is limited in its application. In the first place in patients over forty-five widening of the aortic contour from other causes than syphilis is sufficiently frequent and difficult to differentiate to greatly subtract from the specificity of this finding. In the fifties syphilis of the aorta is almost always combined with arteriosclerosis. In the second place detectable dilatation of the aorta probably occurs only in cases in which the involvement is extensive. It is evident indeed from the study of pathological specimens that not all cases even of extensive aortitis are accompanied by dilatation. It has appeared to be more common in those cases complicated by an aortic insufficiency or accompanied by hypertension. At any rate aortic dilatation is surely often absent in those frequent cases in which the aortitis is limited to a small area in the suprasigmoid region of the aortic wall. The danger of involvement of the coronary orifices or of the aortic valves from such a small focus is unfortunately greater because of proximity, than it is from a more extensive process at a higher level.

The symptomatology at present ascribed to syphilitic aortitis is of very slight diagnostic help. It is for the most part not the product of a careful comparison of clinical observations with pathological findings. It has come down to us from a less critical day and seems compounded of symptoms attributable as much to concurrent coronary ostial stenosis, aortic insufficiency, and even aneurysm as to the aortitis *per se*. There is no doubt, however, that aortitis produces symptoms and it seems very possible that a more intensive clinical and pathological comparison may give us a clinical picture of diagnostic value.

The need for further diagnostic aid in the early detection of aortic syphilis is a very real one. The finding of any syphilitic lesion may unravel many other diagnostic tangles, but especially is it important to discover a lesion so apt to attack vital structures. It now appears probable though not proven that this aortic lesion in its early stages may be controllable by treatment. It seems also established that it is most safely treated not by routine measures but by a more carefully graded use of anti-syphilitic remedies. An improvement in our present methods of diagnosis of syphilitic aortitis will therefore constitute a major contribution to internal medicine.

•

REVIEWS

Clinical Diagnosis Physical and Differential By NEUTON S STERN, A B, M D, Harvard, Associate Professor of Medicine, University of Tennessee School of Medicine, Memphis xvi + 364 pages The Macmillan Company, New York, 1933 Price, \$3 50

Dr Stern has written a textbook that in the reviewer's opinion is most timely. Most textbooks on physical diagnosis either confine themselves solely to the chest organs or are so large and cumbersome that anything like a complete reading constitutes something of an ordeal.

In this book, however, Dr Stern combines completeness with brevity. He crowds an astonishing amount of information into something less than four hundred pages. His description of the mechanisms involved in physical diagnosis is simple, direct and understandable. His outline of laboratory technic is adequate to the requirements of most practitioners and students. His section on the interpretation of symptoms is admirable. He admits with pride that his section on case history teaching has been borrowed from Richard C Cabot. He emphasizes over and over again the value of thoroughness and completeness. The American Heart and Tuberculosis Association's standards of measurements and classification have been adopted, which the reviewer considers a valuable feature.

One hesitates to criticize in any way a textbook with which one is in such marked agreement, but the reviewer feels that in discussing history writing, Dr Stern might perhaps have laid greater emphasis on the past history and have drawn a clearer distinction between the events of the past history and the present illness. A few illustrations would also have enhanced the value of the book.

However, the whole book is so useful and so clear that it deserves to achieve immediate acceptance as a standard text for undergraduate teaching. It cannot fail to be useful to graduate clinicians who wish fundamental information in an accessible form.

T C W

Calcium Metabolism and Calcium Therapy By ABRAHAM CANTAROW, M D, Instructor in Medicine, Jefferson Medical College, with a foreword by HOBART AMORY HARE, B Sc, M D, LL D, Late Professor Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College, Ed II xii + 252 pages, 20 X 14 cm Lea and Febiger, Philadelphia, Pa 1933 Price, \$2 50

The contents of this volume are divided into three general headings: Normal Calcium Metabolism, Abnormal Calcium Metabolism and Calcium Therapy.

In the five chapters which compose the first part of the book such subjects as Calcium Requirement, Calcium Excretion, Blood Calcium and other related topics are discussed. Of special interest in this section is the discussion of the calcium level of the plasma as it is related to the parathyroid hormone and vitamin D. Besides these factors which exercise an important control over the calcium balance of the plasma, the acid-base balance is emphasized. The optimum pH in vitro for calcification is 7.25 to 7.30. Slight calcification occurs at pH 7.00 to 7.10 and no calcification occurs in solutions more acid than pH 7.00. In the form of a recapitulation, the author states that there are five factors which may increase the excretion of calcium, causing a negative calcium balance, and a decalcification of bone: (1) Thyroid Extract, (2) Parathyroid Extract, (3) Vitamin D Deficiency, (4) Excess of Phosphorus, (5) Acidosis.

There are two chapters in Part Two dealing with the abnormalities of calcium metabolism. The hypocalcemiae which accompany many forms of disease are treated

from a theoretical and practical standpoint. The author is especially thorough in his discussions of the influence of various diseases on the character of blood calcium. This is discussed from the point of view of modern physicochemical concepts.

Part Three treats of calcium therapy in its various ramifications. It is gratifying to observe that the author approaches this problem logically, viz., having considered the physicochemical features of blood calcium, the pharmacological are developed next and finally the therapeutics of various calcium salts. The effects of giving calcium salts by the various avenues of administration are compared. After the oral administration of calcium salts lactose is recommended as it enhances the absorption of calcium by increasing intestinal acidity through lactic acid fermentation. The rôle of the active parathyroid extract, prepared by Collip, is discussed in its relationship to calcium therapy. In the author's opinion the discovery of this extract has immeasurably enriched the possibilities of calcium therapy.

The treatise is well written and practically free from typographical errors. The volume fulfills the purpose for which it is intended, namely, to familiarize the clinician with certain aspects of calcium metabolism, and to aid in the establishment of calcium therapy upon a rational basis with full realization of its value and limitations.

J C K, JR

The Duodenum—Its Structure and Function, Its Diseases and Their Medical and Surgical Treatment By EDWARD L. KELLOGG, M.D., F.A.C.S. 882 pages. Paul B. Hoeber, Inc., New York, 1933. Price, \$10.00.

This work true to its substantial title is one of considerable scope and no little value. The author has collected under one cover an enormous amount of data of which the preponderant amount is well selected and correctly interpreted. Naturally in a work of this size there are bound to be subjects on which points of view will differ markedly. The work may be roughly divided into sections dealing with (1) anatomy and physiology, (2) diagnostic technic, (3) a description of the various diseases and disorders that are found in the organ and the indications for their medical and surgical treatment, and (4) a long chapter on surgical procedures.

It is in the third section that the major part of the book's value is to be found. Herein are tabulated in meticulous detail the age, incidence of occurrence, X-ray findings, congenital variations, case histories, etc., appertaining to such subjects as Duodenitis, Abnormalities of Shape and Position, Diverticulosis of the Duodenum, Internal and External Fistulae, Duodenal Hernia, Duodenal Obstructions Caused by Annular Pancreas, Duodenal Ulcer, etc.

The chapter on X-Ray Diagnosis is written by A. Judson Quimby, M.D., and that on Duodenal Parasites by Bailey K. Ashford, M.D. The latter is particularly well done.

As a reference book on the incidence, details and statistics of all types of duodenal abnormalities this volume is particularly recommended.

L M

Peptic Ulcer By JACOB BUCKSTEIN, M.D. Volume Ten of Annals of Roentgenology—A Series of Monographic Atlases. Edited by James T. Case, M.D. 444 pages. Paul B. Hoeber, Inc., New York, 1933. Price, \$12.00.

To the series of Monographic Atlases in Roentgenology has been added the Second Edition of the volume, *Peptic Ulcer*. In it the author presents a series of common and rare roentgenological views of gastric, duodenal, and post-operative gastrojejunal and jejunal ulcers. Interesting historical sketches on the development of radiological technic in each one of these conditions are followed by a large number of films. A case record, short and concise, is given with each photograph.

In addition, valuable, common sense reflections on conditions in which the differential diagnosis is difficult are given, in connection with well chosen illustrations

The work is well planned, well printed and bound. It is well worth a place on one's shelves as a reference volume in peptic ulcer roentgenology

L M

Physical Chemistry of Living Tissues and Life Processes By R. BEUTNER, M.D., Ph.D., Professor of Pharmacology, School of Medicine, University of Louisville. Ed. I. ix + 337 pages, 23 × 15 cm. The Williams and Wilkins Company, Baltimore, Md. 1933. Price, \$5.00

To bridge the gap between inanimate and living matter is the time-honored problem of the basic sciences. Physical chemistry is a powerful tool in the hands of the biologist to shed light upon this fundamental problem. In a masterly manner the author has attempted to elucidate the physical and biological observations which tend to show an analogy between the behavior of inanimate systems and biological processes.

The writer has avoided the mathematical formulae concomitant with physicochemical developments in order to keep the book available to the average student of medicine. However, fortunately for those who are interested in the mathematical development of the field, a mathematical treatment of certain theories has been included in the appendix.

The approach to the problem is divided under three separate headings. First, Membranes, Osmosis and Related Forces are considered; second, Life Processes Related to Crystallization or Owing to Surface Forces are dealt with; and third, Electrical Currents in Tissues and Their Relation to Life Processes are treated. These three main divisions of the book are followed by a chapter on Future Possibilities of Development which deals particularly with Artificial Parthenogenesis.

The reviewer is particularly impressed by the scholarly and philosophic approach to the entire problem which is embodied in the introduction dealing with Life as a Scientific Problem.

Of particular interest to the clinician is the section of the book in which the physicochemical aspects of edema and nephritis are described. Pharmacologists and physiologists will find the Meltzer and Auer's magnesium-calcium antagonism and related phenomena particularly well described.

The style of the author is clear and concise. His statements are in most instances accurate reproductions of original work or careful deductions therefrom. On page 27, it would have been well to point out that cryoscopic measurements involving molecular weight determinations are conducted on the basis of gram-molecular weights in 1000 grams of the solvent and not on the basis of molar solutions. Considering the nice differences between the pH of arterial and venous blood, it is regrettable that nothing is mentioned in this connection on page 74. In the explanation of reversible emulsions, no mention is made of Harkins' orientation theory which provides a brilliant hypothesis for the phenomenon in question.

In its entirety the book fulfills the purpose of the author as previously set forth and points out with convincing assuredness that, "Life in all of its complexity seems to be no more than one of the innumerable properties of the compounds of carbon."

J. C. K., Jr.

The Medical Secretary By MINNIE GENEVIEVE MORSE, Member, Board of Registration, Association of Record Librarians of North America. viii + 162 pages, 11 × 17 cm. The Macmillan Company, New York, 1933. Price, \$1.50.

Although this book is written primarily for the secretary lacking medical training and the nurse to whom secretarial work is new, it will also be helpful and interesting

to secretaries already in the medical field. There are nine chapters: I Qualifications for Medical Secretarial Work, in which stenography and typewriting, medical terminology, correct English, foreign languages, indexing and filing, history-taking, manuscript preparation, mimeographing and multigraphing, handwriting, and miscellaneous office responsibilities are considered; II The Personality of the Medical Secretary, which stresses the importance of dress, manners, tact, initiative and trustworthiness; III Office and Patient, which discusses in connection with the former the reception room, the consulting room, the treatment room and the sterilization of equipment, and in connection with the latter the duties of the nurse or nurse-secretary in the examination and treatment of patients; IV Medical Correspondence, Bills, and Reports, most of which will be merely a review for the person with previous secretarial experience; V Case Records, which should give the unfamiliar an idea of what a hospital case chart and a case history include; VI Medical Indexing and Filing; VII Medical Research, in which "the simplest form of research," the making of a bibliography, is handled rather inadequately inasmuch as, while it gives several styles of listing references, it contains no information as to how to go about looking up references; VIII The Preparation of Medical Manuscripts, which includes a useful group of signs used in correcting proof, and IX Medical Terminology, with a list of medical abbreviations, prefixes and suffixes, and an outline of medical terms compiled "by dividing the body into regions and systems, arranged in alphabetical order, associating with the names of the organs and tissues in each division the names of the principal diseases to which they are liable and the principle operations which may be performed upon them." A bibliography of fifteen books concludes the volume.

M F L

COLLEGE NEWS NOTES

In view of the removal of the Editorial Office of the ANNALS OF INTERNAL MEDICINE to Baltimore, it was found necessary to sever the long and cordial relations which have existed between this journal and the Ann Arbor Press and to place the printing of the ANNALS with a firm in closer proximity to the Editor. Beginning with the present number, the ANNALS will be printed and issued by the Lancaster Press of Lancaster, Pennsylvania. The extensive experience of this firm in printing scientific journals assures us of the continuance of the typographical standards of our journal. With this new volume, certain changes in format have been introduced which the Editor hopes will meet with the approval of our readers.

Acknowledgment is made of the following gifts to the College Library of publications by members:

Dr. Samuel M. Feinberg (Fellow), Chicago, Ill.—1 book, "Asthma, Hay Fever and Related Disorders",
Dr. A. C. Clasen (Fellow), Kansas City, Mo.—2 reprints,
Dr. Henry A. Rafsky (Fellow), New York, N. Y.—3 reprints,
Dr. Walter Clarke (Associate), New York, N. Y.—2 reprints,
Dr. August A. Werner (Associate), St. Louis, Mo.—4 reprints

More than half of the Fellows and Associates of the American College of Physicians residing in the State of North Carolina assembled at a special luncheon at the Sir Walter Hotel, Raleigh, N. C., on April 19th. These round-table luncheons have been held previously by the North Carolina Fellows and are kept entirely to a social plane. Dr. William Gerry Morgan, Secretary General of the College, Washington, D. C., was a guest of honor and spoke informally about the work and activities of the College. Dr. Charles H. Cocke, Asheville, Governor of the College for North Carolina, delivered an address, urging members to maintain the keen interest in the College that they have shown heretofore, and leading a discussion on various aspects of College activities.

Dr. Carl V. Weller (Fellow), Director of the Pathological Laboratories, University of Michigan, Ann Arbor, Mich., spoke before the American Society for Experimental Pathology in Cincinnati, Ohio, during April on the subject of "The Pathogenesis of Trichinosis Myocarditis". Dr. Weller was elected President of that Society for the ensuing year.

Dr. Milton A. Bridges (Fellow), New York City, in collaboration with Ruth L. Gallup, is author of a new book on "Dietetics for the Clinician," recently published by Lea and Febiger of Philadelphia.

Major Edgar Erskine Hume (Fellow), Medical Corps, U. S. Army, Librarian of the Army Medical Library, Washington, D. C., has been elected a Fellow of the Royal Society of Edinburgh.

Dr. Stewart R. Roberts (Fellow), Atlanta, Ga., was recently elected President of the American Heart Association.

Dr James A Lyon (Fellow), Washington, D C , is President of the Washington Heart Association for the current year

Dr F O Mahony (Fellow), El Dorado, Ark , was chosen President-Elect of the Arkansas State Medical Society at its annual meeting at Hot Springs, May 2nd, 3rd and 4th

Dr James Z Naurison (Fellow), Springfield, Mass , has been elected President of the Hampden District Medical Society for 1933-1934

Dr C W Strickler (Fellow), Atlanta, Ga , has been elected President of the Staff of Grady Hospital, Atlanta

At the recent annual meeting of the Medical Society of the State of North Carolina, Dr I H Manning (Fellow), Dean of the University of North Carolina Medical School, succeeded to the Presidency, while Dr P P McCain (Fellow), Sanatorium, was made President-Elect and Dr R L Felts (Fellow), Durham, First Vice-President

Metabolic Disorders will be the theme of the 1933 Graduate Fortnight of the New York Academy of Medicine Two weeks of intensive study from October 23rd to November 3rd, inclusive, will be devoted to this important branch of medical science The theoretical, physiologic and pathologic phases of Metabolism, as well as of certain of the associated endocrinologic problems, will be treated in a series of round-table discussions and clinical demonstrations Among the speakers are the following Fellows of the College

Dr Walter W Palmer, New York City
Dr Emanuel Libman, New York City
Dr Priscilla White, Boston

Dr Fred G Holmes (Fellow), Phoenix, Ariz , was named President-Elect of the Arizona State Medical Association at its annual meeting in April

Dr Arthur C Christie (Fellow), Washington, D C , and Dr Cyrus C Sturgis (Fellow), Ann Arbor, Mich , were guest speakers at the annual meeting of the California Medical Association in April

Dr Joseph D Applewhite (Fellow), Macon, Ga , was elected a Vice-President of the Medical Association of Georgia at its recent annual meeting in Macon

Dr Ernest E Irons (Fellow), Dean of Rush Medical College, Chicago, has been appointed Chairman of the Department of Medicine to succeed Dr George F Dick

Dr Allen K Krause (Fellow), Tucson, Ariz , delivered the annual Trudeau Lecture at the joint meeting of the St Louis Medical Society and the St Louis Trudeau Club during April, his subject being "The Principles of Activity in Pulmonary Tuberculosis"

Dr William E Nesbit (Fellow), San Antonio, Texas, was elected President of the Texas Club of Internists at its spring meeting in Fort Worth during March
Dr Allen K Krause (Fellow), Tucson Ariz was the guest speaker

Dr Julius H Hess (Fellow) and Dr Robert A Black (Fellow), both of Chicago, are among those selected to organize groups of teachers to conduct a one-day lecture course in Pediatrics in eleven districts of Illinois, under the auspices of the American Academy of Pediatrics and the Educational Committee of the Illinois State Medical Society

Dr James B Herrick (Fellow), Chicago, Ill, was elected President of the American Association of the History of Medicine at its annual meeting in Washington during May Dr Herrick succeeds Dr Gerald B Webb (Fellow), of Colorado Springs, Colo

Dr William S Middleton (Fellow), Madison, Wis, was elected a Vice-President, and Dr E J G Beardsley (Fellow), Philadelphia, Pa, Secretary

Dr Francis G Blake (Fellow), Sterling Professor of Medicine in the Yale University School of Medicine, has been appointed Chairman of the Division of Medical Sciences of the National Research Council

Dr Wilmarth B Walker (Associate), Cornwall, Conn, was elected Secretary of the Litchfield County Medical Society at its 169th annual meeting during April

Dr Edward B Vedder (Fellow) was recently appointed full-time Professor of Experimental Medicine and Executive Officer of the Department of Pathology and Experimental Medicine of the George Washington University School of Medicine, Washington, D C

Dr John A Kolmer (Fellow), Professor of Medicine at Temple University School of Medicine, Philadelphia, Pa, was among those selected to conduct a graduate course in Medicine at the University of Florida, June 19th to 24th, under the sponsorship of the Florida Medical Association

Dr Tracey H McCarley (Fellow), McAlester, Okla, has been elected President of the Oklahoma State Medical Association for 1933-1934

OBITUARIES

DR JOHN BLOSS WOLFE

Dr John Bloss Wolfe (Fellow), Wilkes-Barre, Pa, died suddenly at his home on June 1, 1933, from angina pectoris

Dr Wolfe was born at Berwick, Pa, on March 21, 1892. He graduated from the Jefferson Medical College of Philadelphia in 1915 and was Resident Physician at the Episcopal Hospital, Philadelphia, for two years. He was also Resident Physician for several months at the Kensington Hospital of Philadelphia, but entered the military service during the War and was attached to Base Hospital No 34, he was honorably discharged with the rank of Captain. In 1921, he became a member of the Staff of the Wilkes-Barre General Hospital, and at the time of his death was an Associate in Medicine.

Dr Wolfe was active in all forms of medical work as well as civic affairs. He was a member and the Editor of the Bulletin of the Luzerne County Medical Society, a member of the Lehigh Medical Association, a member of the Pennsylvania State Medical Society and a Fellow of the American Medical Association.

He was a lover of the outdoors and very fond of playing golf. He made many trips into the most remote wildernesses of Northern Canada, hunting big game. He leaves a wife and four children, three boys and one girl.

In the death of Dr Wolfe, the medical profession has lost a dear friend and able member, the community, one of its best physicians, and his family, a loving husband and father.

(Furnished by

G E BAKER, M D, F A C P,
Wilkes-Barre, Pa.)

DR WALKER EUGENE STALLINGS

Dr Walker Eugene Stallings, an Associate of the American College of Physicians, died May 6th, at the Fitzsimons General Hospital, Denver, Colo.

Dr Stallings was born at Newport, Ark., February 1, 1896. He attended Valparaiso University one year, Texas Christian University one year and then entered Vanderbilt University School of Medicine, from which he received his medical degree in 1920. He spent one year as an interne at the St. Vincent's Infirmary, Little Rock, Ark., and four additional months at St. Joseph's Infirmary, Memphis, Tenn. At a later date he pursued postgraduate study in tuberculosis and electrocardiography at the Fitzsimons General Hospital. On July 1, 1929, he entered the service of the U. S. Veterans' Administration as Tuberculosis Specialist at the U. S. Veterans' Hospital in Boise, Idaho. He also acted as Consultant in Tuberculosis to the St. Luke's Hospital at Boise and Consultant in Tuberculosis for the State of Idaho, and was in charge of the State Hospital for Tuberculosis.

Dr Stallings was a member of the Idaho State Medical Society, the American Medical Association, the Southern Medical Association and the Denver Sanatorium Association. He became an Associate of the American College of Physicians during 1932.

Dr Stallings' professional standing and ethics were of the highest and he was blessed with a delightful personality.

THE DESERT SANATORIUM OF TUCSON, ARIZONA

ALLEN K. KRAUSE, M.D.,
Director

W. PAUL HOLBROOK, M.D.,
Physician-in-Chief

¶Offers the facilities and services of its splendidly and completely equipped Out-patient Department for the diagnosis and treatment of acute and chronic disease during the summer

¶Caring for both ambulant patients and those confined to bed in quarters outside the Sanatorium

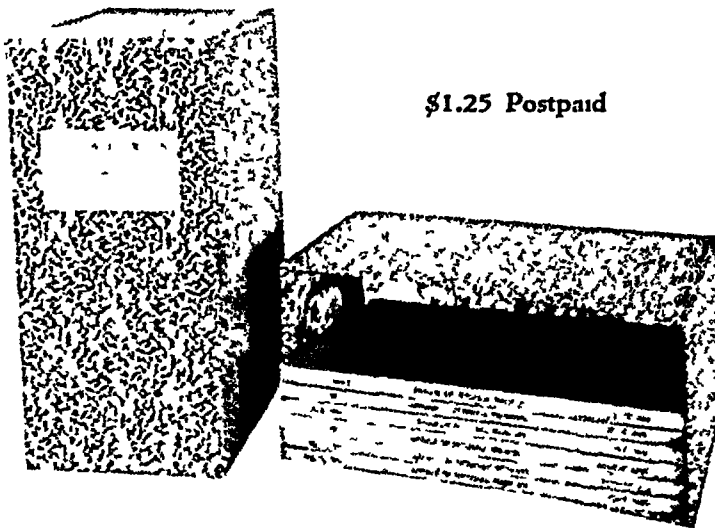
¶Hot, dry, desert climate especially beneficial for chronic sinusitis, pulmonary affections of various types, hypertension, arthritis, etc

¶Special Department of Physiotherapy Heliotherapy, when indicated, administered under proper safeguards

Accommodations obtainable in Tucson and neighborhood

For information and rates, address Miss B. M. Dickey, Administrative Secretary

Volume File for Annals of Internal Medicine



\$1.25 Postpaid

One of these volume files will keep a complete volume of twelve issues of ANNALS always assembled and readily accessible for reference on your bookshelf. Extend the usefulness of the journal through succeeding years. Assemble Volume VI, with its printed index, which was completed with the June, 1933, number. These Vol-

ume Files are especially manufactured for Annals of Internal Medicine, and are durably and neatly constructed. Indexed on the front with name and volume number.

THE AMERICAN COLLEGE OF PHYSICIANS

133-135 S. 36th Street

Philadelphia, Pa.

NATIONAL TETANUS ANTITOXIN



TETANUS ANTITOXIN (National) is highly refined and contains the antitoxic substances precipitated from non essential proteins, euglobulins and inert solids. The exceedingly small bulk insures quick absorption—therefore rapid protection—reduces pain of injection, the small amount of protein present lessens serum reactions.

For immunizing or prophylaxis inject 1500 to 5000 units deep intramuscularly, or subcutaneously, immediately patient reports wound. The period of passive immunity is relatively short and it is therefore advisable—in slow healing and wounds contaminated with debris, particularly following automobile injuries or wounds from fireworks or gun-shot and compound fractures—to give at least two doses of 3000 to 5000 units of tetanus antitoxin at weekly intervals.

Therapeutic doses must be heroic, 40,000 to 100,000 units given intravenously, intraspinally or intradurally at six to twelve hour intervals.

In Perfected Syringes of 1500 units, \$1 88, 10,000 units, \$9 00, 20,000 units, \$16 50

START PRE-SEASONAL TREATMENT OF HAY FEVER NOW

We offer **RAGWEED ANTIGEN** (Fall Hay Fever Antigen)

Prepared from the pollens of giant and dwarf ragweed, standardized in protein-nitrogen units. Complete Treatment No 1 consists of 24 doses (Three 5 cc Ampoule-Vials)

					Net Price	Code Word
V 209	Series "AA" containing	125 protein nitrogen units	(8 doses)			
	Series "A"	250 "	(8 doses)			
	Series "B"	500 "	(8 doses)		\$8 50	ASAF
	Single 5 cc Ampoule-Vials					
V 2091	Series "AA"	125 "	(8 doses)		2 70	SIA
V 211	Series "A"	250 "	(8 doses)		3 75	SIF
V 212	Series "B"	500 "	(8 doses)		4 75	SOL
	For patients requiring higher antigenic potency					
V 215	Series "C" containing	1250 protein nitrogen units	(5 cc ampoule vial)		6 00	SUP

THE NATIONAL DRUG COMPANY
PHILADELPHIA
U.S.A.

Mail

pkgs Tetanus Antitoxin

units

pkgs Ragweed Antigen

No

per Jour A. M. A.

Name

Date

Address

State

Please Mention this Journal when writing to Advertisers

Specific Therapy in Erysipelas

Symmers, comparing 15,277 cases of erysipelas treated without antitoxin over a period of 23 years with 705 cases treated with antitoxin, found an apparent reduction in mortality in serum treated cases of 44.5%. Symmers remarks (J.A.M.A., August 25, 1928) "The antitoxin treatment of erysipelas marks an advance, the results of which are commensurate with those obtained in the treatment of diphtheria."



Parke-Davis Erysipelas Streptococcus Antitoxin is obtained from the blood of horses immunized against the streptococcus from highly virulent cultures of Streptococcus hemolyticus isolated from erysipelas. This antitoxin is refined and concentrated, the antitoxic properties being retained in very small bulk; the product is free from most of the inactive serum constituents.

This antitoxin is subjected to skin tests to determine its potency. Each lot is given rigid bacteriologic tests, both while in bulk and after enclosure in the syringe container to insure sterility.

Supplied in packages of 10 cc and 20 cc syringes (Bios 2010 and 2012)



PARKE, DAVIS & COMPANY

*The World's Largest Makers of
Pharmaceutical and Biological Products*

THE POTTENGER SANATORIUM AND CLINIC FOR DISEASES OF THE CHEST

Monrovia, California



THIRTY YEARS' EXPERIENCE IN THE TREATMENT OF TUBERCULOSIS

LOCATION

Sixteen miles east of Los Angeles In the foothills of the Sierra Madre Mountains, at an elevation of 1000 feet On the main line of Santa Fe Railway Connected with Los Angeles by interurban railway and splendid boulevards

ENVIRONS

The grounds consist of a beautiful park of forty acres, in which are found a variety of native Live Oaks, subtropical trees and plants, and a profusion of beautiful shrubs and flowers Many winding walks and nooks of exquisite beauty add to its attractiveness When on exercise, patients also enjoy the beautiful trails in the adjoining canyons and mountains

MEDICAL CARE

Competent resident staff Examinations for comparison every six weeks Patients visited twice daily Their individual needs and problems receive close personal attention

THERAPEUTIC CARE

Fads are not followed but an endeavor is made to give patients the amount of rest and exercise suited to their individual needs, the benefits of a liberal and adequate diet, such tonic measures as will increase their resistance, and other measures that will help them overcome any disturbing symptoms or complications that may arise Heliotherapy, tuberculin, pneumothorax and surgery employed whenever indicated

DIAGNOSTIC CLINIC

A diagnostic clinic is maintained for the study of all diseases of the chest Weekly rates from \$25 up including medical attention medicines (except expensive remedies) and general nursing Extra charge for operative measures (except pneumothorax)

F M POTTENGER, M D Medical Director

For Particulars Address

THE POTTENGER SANATORIUM, Monrovia, California

The
WYATT CLINIC

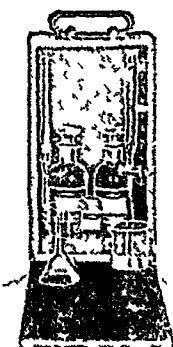
for

Chronic Arthritis

at

TUCSON, ARIZONA

LaMOTTE
Blood Urea Outfit



For study of urea retention (urea nitrogen by factor)

Result is read directly from special Urea Burette supplied

No calculations required

Accurate to 4 mg urea per 100 c c blood

Complete estimation takes only 15 to 20 minutes

Price, complete with instructions, \$18.50 f.o.b. Baltimore, Md

Your LaMotte Blood Chemistry Handbook* illustrates and describes many other simple, accurate testing outfits developed by LaMotte Research Department in co-operation with recognized specialists

*If you do not have one, write today for a complimentary copy

LaMOTTE
Chemical Products Co.

418 Light Street

Baltimore, Md

The
A. B. C.'s
of the Diabetic Diet are
Adequate in Nourishment
Beautiful to the Sight
Correct in Food Value

CURDOLAC
FOODS

fulfill these A B C's perfectly That is the reason diabetics thrive on them

Samples and Literature on Request

CURDOLAC FOOD CO.
Box 299 Waukesha, Wis.

Fellowship Insignia
for
Academic Gown



After exhaustive investigation by the Committee on Insignia, the Board of Regents of the American College of Physicians has officially adopted a cross of the shape of the Fellowship Key, approximately three inches in height, of green velvet with the Seal of the College outlined in gold braid, to be worn at the option of the member on the right side of the academic gown to indicate Fellowship

These insignia, which have been made up and ready to be stitched to the gown may be procured at nominal cost through the Executive Office of the College, 133-135 S 30th Street, Philadelphia, Pa

THE ANALYSIS SHOWS

THE VALUABLE ALKALINE CHARACTER OF

VICHY CÉLESTINS

Natural Mineral Water

INDICATIONS

In stomach and
liver affections
and digestive disorders
in general;
in gout, arthritis
associated with uric
acidemia, uricemia,
and nephrolithiasis of
uric acid origin.



BOTTLED
AT THE SPRING
VICHY, FRANCE

ANALYSIS (GRAMS PER LITER)

Sodium bicarbonate	3.3090
Potassium bicarbonate	0.2490
Lithium bicarbonate	0.0281
Calcium bicarbonate	0.7400
Magnesium bicarbonate	0.1016
Ferrous bicarbonate	0.0012
Sodium chloride	0.3830
Sodium sulphate	0.2430
Silica	0.0300
Sodium arseniate, Phosphate and nitrate	} present

Brochure with Therapeutic Data and Medical Bibliography
sent on request.

Sole United States Agents, American Agency of French Vichy, Inc., 503 Fifth Ave, New York

THE DESERT SANATORIUM OF TUCSON, ARIZONA

ALLEN K. KRAUSE, M.D.,
Director

W. PAUL HOLBROOK, M.D.,
Physician-in-Chief

¶Offers the facilities and services of its splendidly and completely equipped Out-patient Department for the diagnosis and treatment of acute and chronic disease during the summer.

¶Caring for both ambulant patients and those confined to bed in quarters outside the Sanatorium.

¶Hot, dry, desert climate especially beneficial for chronic sinusitis, pulmonary affections of various types, hypertension, arthritis, etc.

¶Special Department of Physiotherapy. Heliotherapy, when indicated, administered under proper safeguards.

Accommodations obtainable in Tucson and neighborhood

For information and rates, address Miss B. M. Dickey, Administrative Secretary

The WYATT CLINIC

for

Chronic Arthritis

?

TUCSON, ARIZONA

SUPPORT Your Journal and its Advertisers



Admittedly the leading journal in the field of Internal Medicine, ANNALS OF INTERNAL MEDICINE should outrank other journals of its kind in circulation and advertising worth!

Members of the American College of Physicians, publishers, can assist in expanding the circulation and enlarging the advertising by recommending the Annals to fellow physicians and libraries for subscriptions, and to high grade advertisers for introducing their products to internists everywhere.

ARTERIOSCLEROSIS

A SURVEY OF THE PROBLEM

Edited by

E. V. COWDRY

Washington University,
St. Louis

A Publication of the
**JOSIAH MACY, JR.
FOUNDATION**



Price
\$5 00

With the publication of this distinguished volume, the doubts and confusion of years have been set aside

International in scope, searching in its treatment, every aspect of the subject has been covered

Contributors

N ANITSCHKOW
LUDWIG ASCHOFF
E. T. BELL
DANIEL BLAIN
CRIGHTON BRAMWELL
STANLEY COBB
ALFRED E. COHN
E V. COWDRY
HERBERT FOX
JONAS S FRIEDENWALD
HOWARD T. KARSNER
FRITZ LANGE
ESMOND R LONG
W G MACCALLUM
GEORGE R MINOT
WILLIAM OPHULS
A POLICARD
PERCY STOCKS
EDGAR SYDENSTRICKER
SOMA WEISS
H GIDEON WELLS
GEORGE DEE WILLIAMS
JOHN H WICKOFF

Comment

"It can be said with confidence that this volume constitutes the most complete, the most authoritative, and the most illuminating and outstanding contribution to the study of Arteriosclerosis yet made. Student, investigator, pathologist, physician at large—all can read it with profit. Without doubt it will remain an outstanding reference work for some time to come."

—*Jl of Laboratory and Clinical Medicine*

Contents

- | | |
|--|---|
| Introduction | XI Chemistry of Arteriosclerosis |
| I Development of our Knowledge of Arteriosclerosis | XII Acute and Chronic Infections as Etiological Factors |
| II Structure and Physiology of the Blood Vessels | XIII Retinal Arteriosclerosis |
| III Physical Properties of Arteries in Health and Disease | XIV Arteriosclerosis of the Brain and Spinal Cord |
| IV Mineral Constituent of Blood Vessels as Determined by the Technique of Coordination | XV Coronary Arteriosclerosis |
| V Statistical Study of Arteriosclerosis | XVI Sclerosis of the Pulmonary Arteries |
| VI Arteriosclerosis in Lower Mammals and Birds | XVII Arteriosclerosis of the Abdominal Viscera and Extremities |
| VII Race and Climate as Possible Factors | XVIII Hypertension in Relation to Arteriosclerosis |
| VIII Nutrition in Relation to Arteriosclerosis | XIX Hereditary Aspects of Arterial Hypertension in Relation to Arteriosclerosis |
| IX. Pathogenesis of Arteriosclerosis | XX Treatment of Arteriosclerosis |
| X Experimental Arteriosclerosis in Animals | XXI Summary |

Order through your dealer or directly from

THE MACMILLAN COMPANY

60 FIFTH AVENUE

NEW YORK

In congestive heart failure

Theocalcin

(theobromine-calcium salicylate)

Council Accepted



Myocardial stimulation
and a potent diuretic
effect is obtained with
1 to 3 tablets t. i. d.

Tablets $7\frac{1}{2}$ grains each,
also Theocalcin powder.

Literature and samples upon request.

BILHUBER-KNOLL CORP., 154 Ogden Ave., Jersey City, N. J.

Exclusively Engaged
in providing

Professional Protection

Thirty-Four Years



The Medical Protective Company
of Fort Wayne, Ind.

WHEATON

:

:

:

:

ILLINOIS

Devitt's Camp, Inc.

ALLENWOOD
PENNSYLVANIA

(Tuberculosis)

*On beautiful White Deer Mountain, 20 miles southeast
of Williamsport, Pa.*

All modern methods of treatment, including heliotherapy, artificial pneumothorax, phrenic exaeresis, Jacobaeus operation, and thoracoplasty

Not operated for profit Moderate rates Modern buildings

Patients given individual attention by experienced physicians and specially trained registered nurses

The following physicians will be glad to examine patients for admittance to Camp

J M ANDERS, M D, Philadelphia, Pa
ISABEL M BALPH, M D, Philadelphia, Pa
E J G BEARDSLEY, M D, Philadelphia, Pa
WARD BRINTON, M D, Philadelphia, Pa
F W J BURGE, M D, Philadelphia, Pa
DAVID A COOPER, M D
DONALD R. FERGUSON, M D, Philadelphia, Pa
JOHN B FLICK, M D, Philadelphia, Pa
JOHN A KOLMER, M D, Philadelphia, Pa
W ESTELL LEE, M D, Philadelphia, Pa
A C MORGAN, M D, Philadelphia, Pa
ARTHUR W PHILLIPS, M D
GEO MORRIS PIERSOL, M D, Philadelphia, Pa
EDWARD R SNADER, JR, M D, Philadelphia, Pa
MERVYN R TAYLOR, M D, Philadelphia, Pa
THOS J VISCHER, M D, Philadelphia, Pa
A S KECH, M D, Altoona, Pa
CHARLES C HABLSTON, M D, Baltimore, Md
CHARLES S AITKEN, M D, Brookline, Pa.
J C ATWELL, M D, Butler, Pa
F DECARIO, M D, Bradford, Pa
J W WOOD, M D, Chester, Pa

JOHN E FRETZ, M D, Easton, Pa
RICHARD R DALRYMPLE, M D, Erie, Pa
JESSE L LENKER, M D, Harrisburg, Pa
H B ANDERSON, M D, Johnstown, Pa
JOHN H ESBENSHADE, M D, Lancaster, Pa
E J WERLE, M D, Meadville, Pa.
CHARLES G CRANE, M D, Newark, N J
W A WOMER, M D, New Castle, Pa
EDWARD S MCSWEENEY, M D, New York City
M THERESA SCANLAN, M D, New York City
STANLEY L WANG, M D, New York City
W R GLENNEY, M D, Pottsville, Pa
R R JONES, M D, Pittsburgh, Pa
C L PALMER, M D, Pittsburgh, Pa
A H COLWELL, M D, Pittsburgh, Pa
HOWARD U MILLER, M D, Reading, Pa
A E DAVIS, M D, Scranton, Pa
H D WILLIAMS, M D, Trenton, N J
B M ALLEN, M D, Wilmington, Del
JOHN MINOR, M D, Washington, D C
J W PEABODY, M D, Washington, D C
H R SCHREIBER, M D, Washington, D C
E W BIXBY, M D, Wilkes Barre, Pa
HARRY M READ, M D, York, Pa

BOOKLET

ROSS K CHILDERHOSE, M D
JOHN S PACKARD, M D
Associate Physicians

WILLIAM DEVITT, M D
*Superintendent and
Physician in Charge*

How Should the Treatment of

LATE SYPHILIS
differ from that of
PRIMARY or
SECONDARY SYPHILIS
?

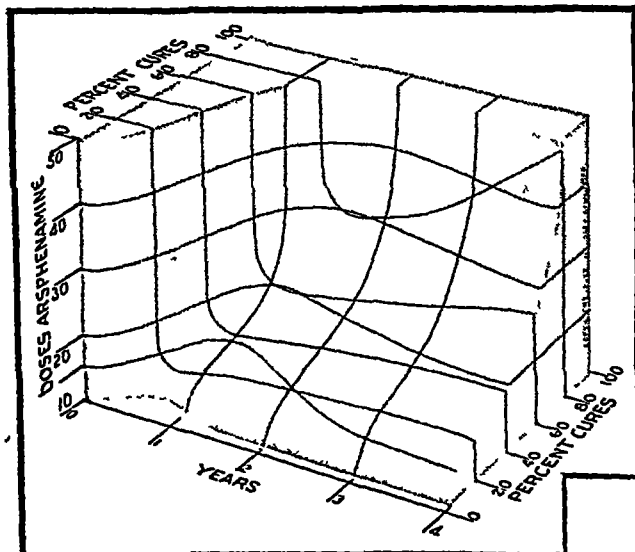


FIG 1—Therapeutic surface Seropositive, primary and secondary syphilis

These Models * Give the Answer

How many doses? How long a period of treatment? What is the percentage expectancy of "cure" if varying amounts of arsphenamine are given over various periods of time? The answers to these questions are graphically and simply portrayed by the form of the surfaces here illustrated

For example, in early syphilis, these figures show quite strikingly the advantage in terms of increased expectancy of cure, of 20 or 30 doses of arsphenamine given in the first year or year and one half of treatment compared with 10 or 15 doses given over the same period of time. They show, too, the importance of a greater time interval in treating tertiary syphilis.

* U. S. - In P. H. S. - 1933 - 1934

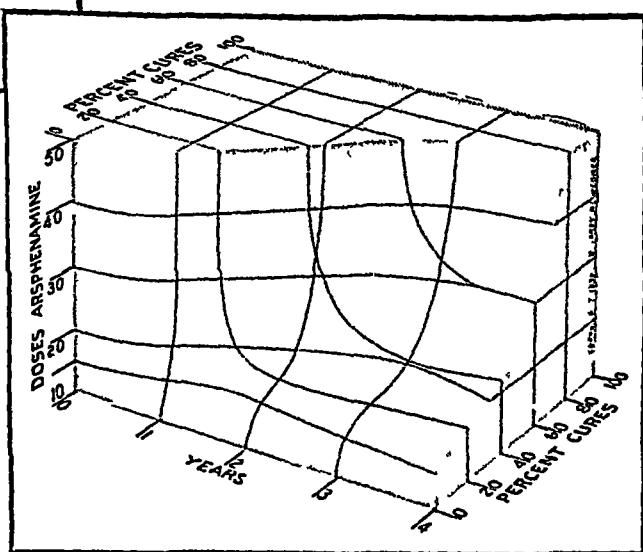


FIG 2—Therapeutic surface Late syphilis

Squibb Arsenicals are designed to provide as great a therapeutic benefit to your patients as is possible. They are uniform in strength, readily soluble and highly spirocheticidal.

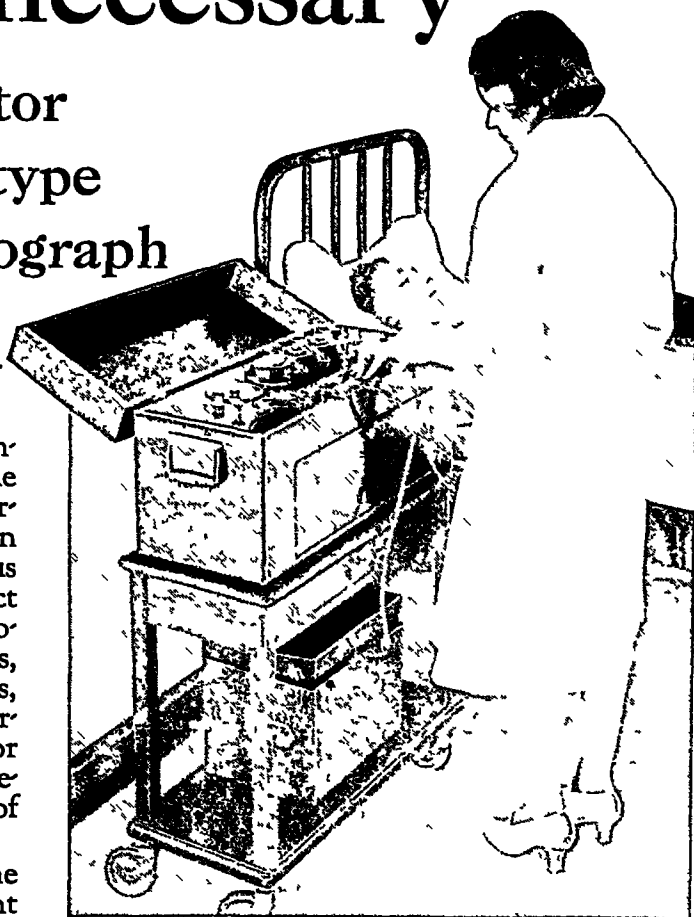
For further information regarding Squibb Arsenicals and their use in the treatment of syphilis, write Professional Service Department, 745 Fifth Avenue, New York.

SQUIBB

A R S P H E N A M I N E
N E O A R S P H E N A M I N E
S U L P H A R S P H E N A M I N E

Compensation for skin current Unnecessary

with Victor
amplifier type
Electrocardiograph



ANOTHER distinct advantage realized with the use of the Victor Electrocardiograph over instruments in which tube amplification is not employed, lies in the fact that there is no need of so-called protective resistances, as used in these other types, to compensate for skin current. Damage to the Victor instrument is impossible, regardless of the amount of skin current.

While it is true that the average patient may present only a small amount of skin current, nevertheless with other types of instruments it must be compensated for, as a part of the regular procedure on each and every patient, before standardization. In other cases the skin current may be of a nature which makes it very difficult, if not impossible, to obtain a perfect record.

Thus, due to the principle of tube amplification as introduced in the Victor Electrocardiograph, another complication in the older procedure is completely eliminated, thereby saving time and further insuring an accurate rec-

With an hour's instruction on the Victor Electrocardiograph, your office assistant can produce heart tracings of unquestionable diagnostic value

ord. Our previous ad in this series explained how the annoying factor of "overshooting" is also eliminated with the Victor instrument. Investigation will show that these and other exclusive features contribute to simplification, reliable performance and consistently accurate heart tracings.

Write for complete information on the new model Victor Electrocardiograph, incorporating a timing device and automatic lead markers, and with which either film or paper may be used.

GENERAL ELECTRIC  **X-RAY CORPORATION**
2012 Jackson Blvd. Formerly Victor X-Ray Corporation Chicago, Illinois

Please Mention this Journal when writing to Advertisers



THEY ARE PACKAGED IN BOTTLES OF THIRTY FIVE A CONVENIENT NUMBER FOR THE PHYSICIAN'S PRESCRIPTION INVOLVING REHANDLING AND EXPOSURE

THE FINISHED PILLS ARE PHYSIOLOGICALLY ASSAYED TO FINALLY CERTIFY THEIR STANDARDIZATION

THE POWDERED LEAF IS TESTED PHYSIOLOGICALLY AND CONVERTED INTO PILL FORM (1 1/2 GRAINS) ON AN AUTOMATIC MACHINE REDUCING EXPOSURE TO THE MINIMUM

A CAREFULLY SELECTED BOTANICALLY IDENTIFIED LEAF, POWDERED IN OUR OWN MILL, GIVING ASSURANCE OF RELIABILITY

THE FOUNDATION UPON WHICH THEY ARE BUILT
AT THE LABORATORIES OF
DAVIES, ROSE & CO., LTD.

The

A. B. C.'s

of the Diabetic Diet are

Adequate in Nourishment

Beautiful to the Sight

Correct in Food Value

**CURDOLAC
FOODS**

fulfill these A B C's perfectly That is the reason diabetics thrive on them.

Samples and Literature on Request

CURDOLAC FOOD CO.

Box 299

Waukesha, Wis.

1933

DIRECTORY

of the

**AMERICAN COLLEGE
OF PHYSICIANS**

A new Directory of the Masters, Fellows and Associates of the American College of Physicians, containing complete alphabetical and geographical rosters, is at press and will be distributed to every member in good standing about September 5.

Seasonal Treatment of Hay Fever

Many hay fever patients neglect to report to their physicians for appropriate pre-seasonal treatment. Some of these have no doubt considered that treatment during the pollen season will afford little or no relief. NINETEEN YEARS' experience with specific pollen antigens has demonstrated to us that relief may be afforded hay fever sufferers even though symptoms have already appeared. Knowing the offending pollen, the physician may administer appropriate desensitizing treatment and in many cases bring about some degree of relief if not complete control of the patients' symptoms.

Information is available concerning those pollens which are chiefly responsible for hay fever in almost every section of America, and if there is any question as to which pollen should be used or as to the best mode of treatment we would invite your inquiries, suggesting that you give in your inquiry the exact geographical location, the exact period of the hay fever, and the symptoms of your patient, particularly as to whether or not asthma is encountered.

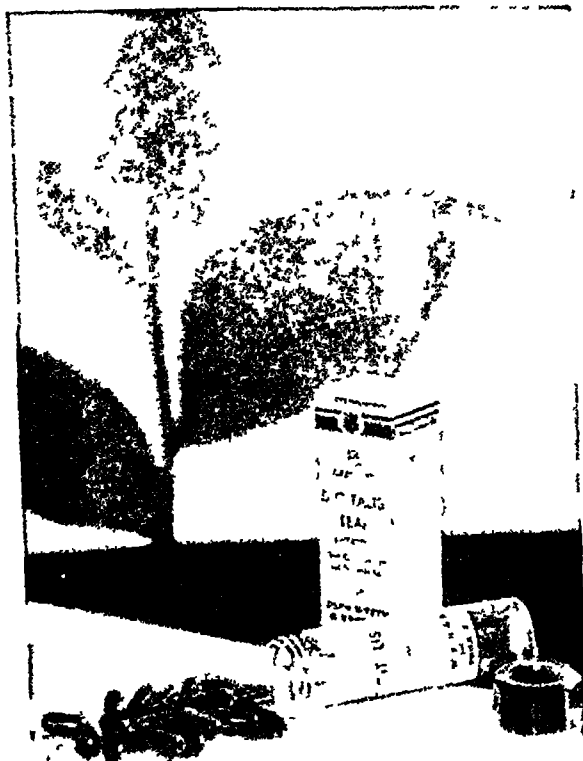
After the treatment for this season has been completed, you may wish to continue with what is termed "Perennial Treatment," that is, the administering of the maintenance dose of the appropriate antigen once each month throughout the year. Such "Perennial Treatment" with Pollen Antigen Lederle overcomes the necessity of repeating the full treatment previous to the following pollen season.

Pollen Antigen Lederle provides the antigen in a medium containing $66\frac{2}{3}\%$ glycerine. In this medium, the antigen is stable so that trustworthy increases in dosage may be made.

Our Department of Allergy solicits your correspondence.

LEDERLE LABORATORIES, INC.
511 Fifth Avenue, New York

DIGITALIZATION



OF THE AMBULANT PATIENT

When the patient has to be constantly digitalized, the capsule form of medication is to be preferred.

The physician can absolutely control dosage, due to the unvarying quantity of drug in each capsule.

The uncertainty and variance in the size of drops, as measured by the patient, is thus eliminated.

No dropper or measuring device being necessary, the convenience for the ambulant patient is also noteworthy.

Wyeth's Capsules Digitalis Leaf (Defatted) are doubly standardized for the protection of yourself and the patient. They are supplied in vials of thirty-six and one hundred distinctive green capsules.

A supply for clinical trial will be sent to you on request.

Control the integrity of your prescriptions
by specifying Wyeth's pharmaceuticals.



JOHN WYETH & BROTHER, INC.
PHILADELPHIA PA AND WALKERVILLE, ONT.



Please Mention this Journal when writing to Advertisers

The Vitamin Question

While the importance of vitamins in the dietary has been recognized for years, the discovery of each new vitamin tends to focus more attention upon that particular vitamin and less upon the others. It is also natural that manufacturers of a product having a high potency of any single vitamin should stress the value of that one above all others.

As research work proceeds, however, not only are new vitamins being discovered, but it is becoming increasingly difficult to separate, definitely, the functions of one vitamin from those of another. For example, investigations appear to show that Vitamin D tends to prevent dental caries and it also appears that Vitamin C is likewise of value in the prevention of tooth decay. It has been shown that an excess of Vitamin D increases the tendency to infection unless the ingestion of Vitamin A is correspondingly increased. Research has indicated that not only Vitamin A, but also the Vitamin B complex is growth promoting. In a word, the sympathetic unity of action of vitamins must have the physician's careful consideration.



In a recent article by Hoobler, entitled, "Use of Vitamin B in Diets of Infants," (Jl A M A, Feb 28, 1931, page 676) he says: "An important research conducted by Harris and Moore (Hypervitaminoses and Vitamin Balance an Instance of Vitamin Balance,

Biochem, J 23 1114) showed that there exists a definite balance among Vitamins E and G, by greatly increasing Vitamins A and D in diets, an otherwise adequate amount of Vitamin B is made inadequate, leading to death of animals. One should be careful not to overdose with cod liver oil and viosterol unless at the same time an increasing quantity of Vitamin B is also added to the diet."

This work indicates the advantage of administering a generous amount of the four vitamins, A, B₁(f), B₂(g) and D in one nutritive, palatable combination. MALTINE WITH COD LIVER OIL is biologically standardized and guaranteed to contain these four vitamins. Biological report on request. The Maltine Company, 30 Vesey Street, New York.



Council Accepted

Calcium Deficiencies IN TUBERCULOSIS

IN a study of 154 tuberculous patients Kaminsky and Davidson¹ found low calcium values to be more frequent than in normal subjects. Crimm suggests that a slight hypercalcemia may be desirable in the treatment of tuberculosis and employs viosterol for the purpose.²

Spies³ and Levaditi and Po⁴ found in experiments that viosterol has the special property of calcifying the necrotic and caseous portions of the tubercles. The latter state that a calcium shell is formed, probably the bacteria-inhibiting factor.

Hildebrand⁵ notes that where the incidence of rickets is high, that of tuberculosis is likewise. Grant, et al,⁶ have shown ricketic rats to be more susceptible to tuberculosis than are non-ricketic animals. Bergmann⁷ finds that both rickets and tuberculosis respond to treatment with irradiated ergosterol. Menschel speaks highly of viosterol for tuberculosis, stating that it inhibits the exudative processes and also checks night sweats, fever, and hemorrhages.⁸

Present-day thought on calcium

therapy in tuberculosis is well summarized by the following statement in the *Journal of the American Medical Association*.⁹

"In previous years certain chemical substances—principally the creosote series—were used to inhibit the growth, or to destroy, tubercle bacilli in the body. Tuberculosis workers have learned the inadequacy of such measures and these substances have been discarded almost entirely. It is felt that the improvement in the patient, consequent on the taking of a balanced dietary, with an adequate amount of mineral salts and vitamins, allows of an increased phagocytosis, which increases the destruction of tubercle bacilli. The improved condition of the tissues also enables not only a resorption of the inflammatory exudate in tuberculosis but a walling off of the tuberculous process, thereby preventing the spread of such disease. Calcium therapy in tuberculosis is considered one of the most important considerations. Calcium absorption is apparently dependent on the vitamin D function in the body."

MEAD'S CEREAL

Enriched with mineral and
vitamin containing foods

SUPPLIES Calcium

Two ounces of this delicious food furnishes as much calcium as 12 ounces of milk, thus obviating the need for large intake of milk, with its concomitant danger of diminishing appetite and inducing anemia. Rich in vitamin B, Mead's Cereal increases appetite, and it is the highest source of food iron, important considerations in tuberculosis. Crimm¹² has shown its value in increasing the weight of tuberculous children.

MEAD'S VIOSTEROL

IN OIL 250 D

UTILIZES Calcium

It offers the most reliable, the most rapid means of increasing calcium concentration of the serum when deficiencies exist. Crimm² has shown that Mead's Viosterol is effective in maintaining the calcium-phosphorus product of the serum at a high level in tuberculosis. Mead's Viosterol is uniformly potent, accurately assayed, packed in brown bottles and light-proof cartons.

¹³ Bibliography on request.

MEAD JOHNSON & CO., Evansville, Ind., Pioneers in Vitamin Research

* This is a report of the prepared form as it appears. It is to be used by adding to it (with a fork) with water as much as is desired. The whole is prepared in the cereal bowl in a few moments.

Please Mention the Journal when writing to Advertisers

ANNALS OF INTERNAL MEDICINE

VOLUME 7

AUGUST, 1933

NUMBER 2

ASPECTS OF CARBOHYDRATE AND FAT METABOLISM *

By C H Best, M D , *Toronto, Canada*

IT WOULD be a very easy matter to discuss recent work on carbohydrate and fat metabolism at great length from the experimental point of view. There are also numerous points of considerable clinical interest. I might gather these latter together and refrain from any description of our own researches, but this would not be fulfilling the obligation which I was very pleased to accept when invited to present this paper. I will, however, compromise and discuss briefly certain general aspects of the subjects and also the results of some investigations which we are at present pursuing.

In the short time at my disposal a few comments on the various phases from the ingestion to the final disposition of the carbohydrate will have to suffice. It is now a matter of common occurrence to observe the great rapidity with which ingested carbohydrate can be absorbed. The effect on blood sugar can actually be detected within a minute or two after the sugar enters the duodenum. Clinicians observe the results of this phenomenon when ingested sugar dramatically relieves insulin hypoglycemia. Cori's recent work (1931) indicates that the different monosaccharides are absorbed at a characteristic and constant rate which is independent of the concentration of the monosaccharide in the intestine. This is quite different from the rate of absorption of the same sugars administered intraperitoneally (and, one presumes, subcutaneously), in which case the rate of absorption is a function of the concentration of the sugar. Cori's results suggest that the presence of other sugars would diminish the rate of absorption of dextrose from the intestine. If this is true, dextrose theoretically should not be mixed with other sugars when the most rapid absorption is desired. From a practical point of view the difference of rate is probably of little significance in most cases. When the sugar is absorbed it passes first, of course, to the liver, where glycogen may be formed. Endogenous insulin also passes first to the liver. The glycogenic and other functions of the liver may be facilitated during digestion by an accumulation of blood in this organ produced by constriction of the hepatic veins and dilatation of the

* Read before the American College of Physicians, Montreal, Canada, February 7, 1933
From the Department of Physiology, University of Toronto

portal system The recent results of Bauer, Dale, Poulsson and Richards (1932) suggest the possibility that vasodilator materials either absorbed from the intestine, or perhaps produced in the liver, may be responsible, in some species, for this accumulation of blood It is interesting that the liberation of adrenalin which, for example, might accompany strenuous muscular exercise or excitement, would probably produce a dilatation of the hepatic veins with the resulting emptying of the accumulated blood from the liver, and perhaps an interference with hepatic function The rise in blood sugar which accompanies the absorption of carbohydrate elicits an increased liberation of insulin from the islet cells The exact mechanism of action of the sugar is still debatable, but if we accept the experimental results of La Baire and Zunz (1927, 1929, 1930) evidence would be available that the sugar acts by stimulation of the parasympathetic centers in the hypothalamic region of the brain The sugar is said to produce no effect after section of the vagus nerve, or paralysis of the vagus endings in the pancreas, by the use of atropine From a morphological point of view we would expect the right vagus nerve to exert some effect on the islet cells, since this nerve sends fibers to the pancreas, which are distributed in close proximity to and may even pierce the accumulations of islet tissue We cannot accept, however, at the present time, the conception that sugar must always act by the stimulation of vagus endings until some further evidence is secured that there are functioning vagus endings in an apparently denervated pancreatic remnant On the other hand, it is certainly not established that this pancreatic remnant permits normal glucose tolerance, and that it does not merely liberate more or less continuously a very small amount of insulin Unfortunately at present we have no method of measuring exactly the insulin content of blood, but it has been satisfactorily established by physiological procedures that the output of insulin from the pancreatic vein is definitely augmented when the concentration of the sugar in the blood is raised It would seem, therefore, that if it is desired to decrease the strain upon islet tissue some consideration should be given to the level of blood sugar throughout the twenty-four hours, with a view to determining the length of time during which this is above the normal figure One may suppose that the longer the period the level is above the normal, the greater the stimulation of the islands of Langerhans We have no data which enable us to decide whether or not the intensity of stimulation is proportional to the level of hyperglycemia However, one might expect that 50 grams of ingested sugar would cause much greater stimulation of insulin liberation than the amount of protein which would enable 50 grams of sugar to be manufactured over a period of time within the body If the formation of sugar from fat takes place, it is probably a gradual process There are grounds for believing that one of the explanations of the apparently beneficial effect of very high carbohydrate diets may be the liberation of insulin If the diet continues to be satisfactory for long periods the stimulation of islet cells may, of course, be considerably reduced In some cases when carbohydrate in excess of that pro-

vided in the adequate diet for a normal person is allowed, the beneficial effect does not persist. Now, there is satisfactory evidence that the insulin which is liberated from the islet cells not only increases glycogen formation in the liver, but also inhibits the new formation of sugar from protein, and probably from fat, in that organ. Contrary to the frequently quoted view, accumulation of glycogen in the liver may take place even though there is an abundance of fat present, and vice versa. There are numerous reports in the clinical literature and some experimental evidence to suggest that a glycogen-rich liver is able to function better and to resist deleterious influences to a greater degree than one which is poor in glycogen. It is easy to demonstrate in diabetic animals that excessive fat deposition in the liver is accompanied by profound interference with sugar formation and other hepatic functions. We have found it possible to decrease glyconeogenesis in diabetic animals to such an extent by adding fat to the diet that the blood sugar sinks to within the limits found in normal animals. The liver becomes intensely fatty and the animal may die suddenly. The point I wish to make here is that apparently beneficial effects may be produced in the diabetic by procedures which are fundamentally injurious.

Now, of course, liver glycogen formation does not account for nearly all the sugar which disappears under the action of insulin. Accumulation of this carbohydrate reserve in muscle is also easy to demonstrate. The evidence at present strongly suggests that insulin is not, however, necessary for the formation of small amounts of glycogen in muscle (Cori, 1929, and Major and Mann, 1932). There can be no doubt, however, that insulin greatly increases the rate at which sugar is converted into glycogen in muscles and, indeed, under some conditions in experimental animals insulin is the deciding factor. It has been stated by Hoet and his co-workers (1931) that glycogen broken down by muscular contraction is not resynthesized in muscle after the vagi are cut. In other words, it is thought that the liberation of insulin from the pancreas is absolutely necessary for the resynthesis of glycogen under these conditions. It appears probable from the work of Long and Horsfall (1932) that the formation of glycogen from glucose under the action of insulin favors the formation of glycogen from lactic acid, i.e. favors the recovery of muscle from exercise. There is evidence that there is accumulation of muscle glycogen during some phases of the change in muscle which accompanies physical training. All these points emphasize the importance of insulin in muscle metabolism and excite our curiosity concerning the magnitude of the disturbance produced when there is not complete absence, but only an insufficiency of insulin production, or a partial inactivation of available insulin by the products of infection such as may occur in many clinical cases. These findings are of considerable interest also in the interpretation of the beneficial results which follow intravenous glucose in so many clinical conditions. The glucose solution, in addition to supplying fuel and water, would liberate insulin and cause or facilitate the changes in liver and muscle which I have described.

If I were able to add much to the obvious facts concerning the effects of infection on carbohydrate tolerance I would discuss the subject fully. Experimentally it can be shown that liberation of adrenalin and possibly thyroxin is one of the effects of the products of bacterial action. Quite recently Murray and Waters (1932) have shown that the insulin content of the pancreas is lowered in infected animals. This does not necessarily mean that the rate of liberation from the pancreas is reduced, but the result encourages us in the attempt to determine whether or not this is the case.

Increased oxidation of carbohydrate in diabetic animals undoubtedly accounts for a part of the sugar which disappears under the influence of insulin. A great deal of experimental evidence establishes the fact that the oxidation of carbohydrate is not in abeyance even in the completely depancreatized animal (Soskin, 1931).

We know that the fatty acid content of blood and tissues of diabetic animals can be decreased by insulin administration. The ketone bodies are, of course, brought to within normal limits by the appropriate use of this substance. Instead of discussing in further detail these well-known effects of insulin on fat metabolism, I will spend what time remains to me in describing the present position of a certain problem in fat metabolism which happens to be my own major research interest at the moment.

The research which I am going to discuss deals in large part with the health of the members of a colony of diabetic dogs which have been observed continuously in the Department of Physiology since 1921. The original members of this colony were, of course, those upon which the experiments leading to the isolation of insulin were conducted. These diabetic animals were our only test subjects until Collip's studies on normal rabbits made that species available. The rise in oxygen consumption and in the respiratory quotient of a diabetic animal when insulin and sugar were given (observed by Hepburn and myself) provided the first evidence that the combustion of carbohydrate was actually increased by the administration of insulin. Storage of liver glycogen and lowering of liver fat by insulin were first demonstrated in these diabetic dogs. The excretion of ketone bodies in these animals was definitely reduced by the administration of insulin. Symptoms of insulin hypoglycemia were observed and described in the diabetic dog but were not attributed to the low blood sugar until after studies on rabbits had been conducted. The glucose equivalent of insulin was carefully determined in depancreatized animals by Allan (1924), who found that when the carbohydrate ingestion was constant the glucose equivalent per unit became progressively smaller as the dose was increased. When the amount of insulin was kept constant and the carbohydrate was increased, the glucose equivalent of the insulin rises up to a certain point and from then on is practically constant. This finding accounts in part for the favorable results obtained clinically with diets higher in carbohydrate. The interrelationship of phosphate and carbohydrate in the metabolism of diabetic animals was suggested by Solley and Allan (1924) and by Markowitz

(1926) A great variety of anti-diabetic substances have been tested on these diabetic dogs. It is possible to control the diet of the animals accurately and to eliminate subjective effects completely. For these reasons the diabetic animal is perhaps the most suitable subject for the investigation of the anti-diabetic action of any material. Intarvin, synthalin, various extracts from plant sources, liver fractions and so on have been tested, and in the cases mentioned no evidence of any therapeutic effect was secured. It has been found possible to keep these diabetic animals alive for what may be considered an indefinite time. The dog which Banting and I observed for 70 days could undoubtedly have been kept in good condition for a much longer period of time, but we wished to verify the completeness of the pancreatectomy. We observed no abnormal signs in the animal which insulin failed to alleviate. In later experiments, however, Allan, Bowie, Macleod and Robinson (1924) found that depancreatized dogs receiving sufficient insulin and a lean meat and sugar diet, did not keep in good condition indefinitely, but this could be achieved when the diet included raw pancreas. These observers could not, of course, be certain of the mechanism of action of the raw pancreas. Since the characteristic pathological finding in the animals was a fatty infiltration and degeneration of the liver, they debated the possibility that the effect of the raw pancreas might be due to the provision of lipase, in the absence of which fat liberation might have been deleteriously affected. The idea that toxic products may have been formed from undigested protein in the intestine was also considered. While the possibility was mentioned that some chemical substance necessary for the proper metabolism of fat might have been supplied in the minced pancreas, no experiments to investigate this were conducted at that time. Inspired by Leathes' theories concerning the significance of lecithin in fat metabolism, Hershey (1931) tried the effects of adding crude lecithin to the diet of these animals, with most interesting results. To make a long story short, I believe that sufficient evidence has now been accumulated to show that lecithin is able to prevent the development of fatty livers in these animals. Furthermore, we have found that the onset of the fatty condition can be accelerated by adding fat to the diet. In experiments on normal rats, Miss Huntsman, Mr Hershey and I (1932) have obtained evidence that the active constituent of the lecithin is choline. In several instances Ferguson, Hershey and I have obtained evidence that choline will prevent or modify the fatty changes in the livers of depancreatized dogs, but we still have a great deal to learn concerning this matter. We are at present investigating the rôle of choline in fat metabolism in two series of experiments on these dogs. In the first series we are producing fatty livers by withholding any source of choline. A small lobe of liver is then removed for analysis and histological study. If the liver is very fatty, choline is supplied, and the second operation is done when choline has been given an opportunity to produce its effect. As I have said, the results thus far obtained would indicate very definitely that choline is preventing fatty changes in the livers of these animals. In the

second series of experiments we are studying the effect of choline upon fat tolerance curves, but cannot predict what the results of this investigation will be. I will just pause here to mention that surprisingly little is known about fat tolerance and that the field is well worth further exploration both clinically and in experimental animals. In conclusion it is important to note that the fatty changes in the livers of normal rats can be prevented by an oxidation product of choline, betaine, which has no pharmacological properties (Best and Huntsman, 1932). Furthermore, fatty changes in the livers of rats produced by cholesterol can be inhibited by choline (Ridout and Best).

Experiments with diabetic dogs are tedious, and the assistance of patient collaborators and technical assistants is indispensable. I may say, however, that when a clear-cut experimental result is obtained, one feels as a result of previous experience that it can be applied with much more assurance to the treatment of the human diabetic than results obtained in normal animals of the same or of other species.

BIBLIOGRAPHY

- ALLAN, F. N., BOWIE, D. J., MACFOD, J. J. R., and ROBINSON, W. L. Behavior of de-pancreatized dogs kept alive with insulin, *Brit. Jr. Exper. Path.*, 1924, v, 75-83.
- ALLAN, F. N. The glucose equivalent of insulin in depancreatized dogs, *Am. Jr. Physiol.*, 1924, lxxii, 275-290.
- BAUER, W., DALE, H. H., POULSSON, L. T., and RICHARDS, D. W. Control of circulation through liver, *Jr. Physiol.*, 1932, lxxiv, 343-375.
- BEST, C. H., HERSHMAN, I. M., and HUNTSMAN, M. E. Effect of lecithine on fat deposition in liver of normal rat, *Jr. Physiol.*, 1932, lxxv, 56-66.
- BEST, C. H., and HUNTSMAN, M. E. Effects of components of lecithine upon deposition of fat in liver, *Jr. Physiol.*, 1932, lxxv, 405-412.
- CORR, C. F. Mammalian carbohydrate metabolism, *Physiol. Rev.*, 1931, xi, 143-275.
- CORR, C. F., and CORR, G. T. The fate of glucose and other sugars (mannose, fructose, dihydroxyacetone) in eviscerated animals, (Abstr.) *Am. Jr. Physiol.*, 1929, xc, 317.
- HERSHMAN, I. M., and SOSKIN, S. Substitution of "lecithin" for raw pancreas in diet of depancreatized dog, *Am. Jr. Physiol.*, 1931, xcvi, 74-85.
- HOTZ, J., and ELVOLD, H. Compt. rend. Soc. de Biol., 1931, cxvii, 921. La reconstruction du glycogène musculaire après travail est une fonction insulémique, *Compt. rend. Soc. de Biol.*, 1931, cxviii, 436.
- LE BAILLY, I. Sur les modifications de l'insulinémie physiologique après section de la racelle allongée, *Compt. rend. Soc. de Biol.*, 1929, cxv, 962-964.—Role of central nervous system in control of pancreatic secretion, secretion of insulin during hyperglycemia, *Am. Jr. Physiol.*, 1930, xciv, 13-16.—Role of central nervous system in control of pancreatic secretion, external secretion of pancreas during hyperglycemia, *Am. Jr. Physiol.*, 1930, xciv, 17-21.
- LOVE, C. N. H., and HERSHMAN, I. M., Jr. Recovery process after exercise in mammal, conversion of lactic acid into muscle glycogen, *Jr. Biol. Chem.*, 1932, xcvi, 715-731.
- MAYER, S. G., and MAYER, I. C. Formation of glycogen following pancreatectomy, *Am. Jr. Physiol.*, 1932, xcvi, 479-481.
- MAYER, S. G. The effect of phosphate and carbohydrate metabolism. III. The effect of phosphate on the formation of glycogen in depancreatized dogs, *Am. Jr. Physiol.*, 1932, xcvi, 527-531.

- MURRAY, D W G, and WATERS, E T The effect of infection on the insulin content of the pancreas, *Trans Roy Soc Canada*, 1932, xxvi, sec V, 169
- RIDOUT, J H, and BEST, C H Unpublished data
- SOKHEY, S S, and ALLAN, F N The relationship of phosphates to carbohydrate metabolism I The relationship of the changes in phosphate excretion caused by insulin and sugar, *Biochem Jr*, 1924, xviii, 1170-1184
- ZUNZ, E, and LA BARRE, J Sur l'augmentation de la teneur en insuline du sang veineux pancreatique apres l'hyperglycemie provoquee par injection de glucose, *Compt rend Soc de Biol*, 1927, xcvi, 421-423 — Sur la sensibilité des centres nerveux superieurs à l'hyperglycémie provoquee par injection de dextrose, *Compt rend Soc de Biol*, 1927, xcvi, 1400-1403

THE ANALYSIS OF HIGH CALORIC DIETS IN RELATION TO WEIGHT CHANGES*

By J M STRANG, M D , and A B Cox. B S ,

Pittsburgh, Pennsylvania

FOR A PERIOD of four years, we have studied the treatment by dietary measures of patients who were underweight. The principles underlying this treatment and the clinical results have been summarized in a previous paper.¹ Eighteen patients were studied on the metabolic pavilion of the Western Pennsylvania Hospital for periods varying from two to 13 weeks. On 16 subjects of this series the detailed data of the food taken in are sufficiently complete to permit analysis. The analysis of these diets with reference to the weight changes which were observed forms the subject of this present study.

METHODS

The methods for the estimation of food intake were the standardized procedures which have been in use for several years. For these special study patients, all food was weighed on a balance to the nearest 1 gram. Food which was returned was reweighed and subtracted from the initial value. The menus for these patients consisted of only the simple foods, served in a simple manner in order to facilitate the accurate estimation of food eaten but more especially of food returned. Water was supplied in any desired amounts from weighed bottles which were provided with two-holed rubber stoppers through which appropriate glass tubes passed. The figures for the analyses of the several foods were taken for the most part from Atwater and Bryant,² Sherman,³ Waller,⁴ Friedenwald and Ruhrah,⁵ and a few analyses of our own (unpublished). No group analyses were used.

In construction of the diets of this series, due care was taken to supply ample quantities of the various accessory food substances. No details are available but it is felt that all possible needs were liberally supplied. Many of these patients received medication for some time during their stay. Strict account was kept of all medicines used. The total weight taken and the estimated caloric values of the drugs and more particularly of their vehicles were noted. In most cases the calories thus provided formed an insignificant portion of the average intakes. One patient, however, obtained 1500 calories per day from this source.

The figures which appear in the tables are the averages for the entire period of observation of the individual patients. Although six patients were studied for only two to three weeks, six patients stayed for six weeks.

* Read before the Medical Society of the Western Pennsylvania Hospital, June 11, 1932. From the Medical Service of the Western Pennsylvania Hospital.

or more. The average length of stay was 5.4 weeks. It was, of course, impossible for persons to eat exactly the same daily intake over these long periods. Considerable variation was noted from day to day. These variations were most marked in patients who were subjected to diagnostic procedures such as cystoscopic examinations. Intercurrent infections also required temporary departures from the desired routine. Such fluctuations in intake are reflected temporarily in body weight. For example, patient 1 took in only 608 calories on one day and lost 700 grams of weight in this same period. It should, however, be recognized that shifts in water balance are chiefly responsible for these daily weight fluctuations.

Body weight observations were made under standard conditions at 7 a.m. daily. In order to minimize the numerical influence of water shifts, the initial and final weights which are recorded in the tables represent the respective average weights of the day before, day of, and day after the designated date. However, even with these precautions, the short experiments are undoubtedly much more affected by water shifts than the longer studies, as indicated by the marked deviations of the figures for weight gain per 100 extra calories of patients 3 and 14 who were observed for only three weeks (Table 8, Column 8).

OBSERVATIONS

The analysis of the average figures for the food eaten by these patients appears in detail in table 1. The 16 patients averaged 3320 ± 500 calories

TABLE I
Average Composition of High Caloric Diets

1	2	3	4	5	6	7	8	9	10	11	12
Patient	Total cal- ories	Protein			Carbohydrate			Fat			FA/ / G
		Gm	Cal	% Total Cal	Gm	Cal	% Total Cal	Gm	Cal	% Total Cal	
1	2790	42.8	171	6.1	248	992	35.6	175	1627	58.3	61
2	2310	56.0	224	9.6	211	844	36.5	134	1246	53.9	57
3	2850	53.0	212	7.4	228	912	32.9	186	1729	60.5	69
4	3200	62.3	250	7.8	275	1100	34.4	199	1851	57.8	63
5	2980	57.8	231	7.7	51	204	6.8	274	2549	85.5	2.44
6	5090	115.5	462	9.0	399	1596	31.4	326	3033	59.6	69
7	3280	74.9	300	9.1	286	1144	34.9	197	1832	55.9	61
9	3430	70.5	282	8.2	284	1136	33.1	217	2018	58.7	65
10	3200	55.8	223	6.9	219	876	27.4	226	2102	65.7	83
12	3310	47.0	188	5.7	79	316	9.5	302	2808	84.8	2.14
13	3450	45.7	183	5.3	41	164	4.8	333	3096	89.9	3.17
14	3060	70.0	280	9.1	241	964	31.5	195	1814	59.2	67
15	3260	55.6	222	6.8	253	1012	30.9	219	2037	62.3	73
16	3310	62.5	250	7.5	226	904	27.3	232	2158	65.1	83
17	2800	76.3	305	10.7	229	916	32.7	170	1585	56.6	65
18	4790	87.9	352	7.4	371	1484	31.0	317	2949	61.6	72
Average	3320	64.6	258	7.7	228	910	27.5	231	2152	64.7	1.04

per day This figure includes the two patients, 6 and 18, who maintained the phenomenal intakes of 5090 and 4790 calories per day for six and seven weeks respectively If these two extraordinary cases are omitted, the average of the 14 more ordinary subjects is 3090 ± 250 calories per day.

The distribution of this food intake into the three principal groups shows great case variation The protein intake was, however, rather uniform Most of the patients were ordered 1 gram protein per kilogram ideal weight The average intake was 65 grams which provided 7.7 per cent of the total calories The individual intakes varied from 43 to 116 grams while the percentage of total calories varied from 5.3 to 10.7 per cent In this connection it may be mentioned that roughly half of the protein intake was made up of animal proteins of high biological value

The amount of carbohydrate in the diets averaged 228 grams which provided 27.5 per cent of the total calories Three patients were placed upon low carbohydrate rations in which 40 to 80 grams per day were given Although only 5 to 10 per cent of the total calories were provided by carbohydrate, these patients gained weight in a satisfactory manner It may, however, be noted in table 3, column 13, and table 8, column 8, that the respective rates of weight change and the rates of change per 100 extra calories for these patients are among the lower values

The fat content of high caloric diets must of necessity be high, 64.7 per cent of the calories were derived from fat although the actual average weight of fat was no greater than of carbohydrate One patient received 90 per cent of her intake as fat, two others 85 per cent The majority of patients, however took between 55 to 65 per cent It is of interest that the majority of patients ate slightly more carbohydrate than fat and that the two patients with exceptionally high total intakes, ate 50 to 60 grams more carbohydrate per day than fat

The relative amounts of potentially ketogenic and anti-ketogenic substances in these fattening diets are of considerable interest Three patients were given fatty-acid-glucose ratios of 2.14, 2.44, 3.17, respectively These diets were adequately handled without observable ketosis This observation is in accord with the experience which has developed during the reduction of obese patients, namely that normal cells will adapt themselves to handle any ratio of ketogenic to anti-ketogenic substances which may be brought to them The average ratio for the entire group was 1.04 If, however we consider the 13 patients whose ratios ranged from .57 to .83, it will be seen that the more ordinary diets had an average ratio of .68

It might, a priori be supposed that diets containing large quantities of concentrated foodstuffs might introduce large quantities of acid materials and burden the excretory system Such, however does not appear to be the case The acid-base balance of course, varies considerably with the composition of food which are ingested It is a profitless burden to determine the acid-base balance for the 100 days of study Typical menus have been presented for 2070, 3000, and 4000 calorie diets The distribution of the acid-base balance is recorded in the usual terminology in table 2

TABLE II
Acid-Base Balance of 2000, 3000, and 4000 Calorie Diets

1	2	3	4	5	6	7	8	9	10
Food	2000 Calories			3000 Calories			4000 Calories		
	Gms	Excess acid c c	Excess base c c	Gms	Excess acid c c	Excess base c c	Gms	Excess acid c c	Excess base c c
Oatmeal	120	2 35		120	2 35		120	2 35	
Cream	100		60	200		1 20	400		2 40
Egg	50			50			50		
Bread	90	6 07		120	8 10		140	9 45	
Butter	29			106			127		
Orange	125		7 01	150		8 41			
Apricots	120		8 16	150		10 20	200		13 60
Pears	125		4 50	150		5 40			
Potato	200		13 60	200		13 60	200		13 60
Asparagus	100		81	100		81	100		81
Celery	50		3 89	50		3 89	50		3 89
Tomato	50		2 80	50		2 80	50		2 80
Cauliflower	100		5 33	100		5 33	100		5 33
Carrots	100		10 80	100		10 80	100		10 80
Peas	100		1 30	100		1 30	100		1 30
Sirloin	90	11 26		60	7 50		45	5 63	
Roast veal	90	12 16		65	8 78		45	6 08	
Sugar	20			40			60		
Bacon				30	1 60		40	2 08	
Banana							150		8 34
Cherries							150		6 60
Total		31 84	58 80		28 33	63 74		25 59	69 47
Balance			26 96			35 41			43 88

It is noteworthy that in this series of diets the amount of base is roughly twice that of the acid. Also the proportion of base increases with the increase in calories. It should, of course, be recognized that this phenomenon is dependent upon this particular selection of foods and is not necessarily applicable to other menus. It appears to be true, nevertheless, that in the vast majority of the high calorie diets which we have employed, the amount of base far exceeds the amount of acid.

It is of interest to note the bulk of food which was eaten by these patients in relation to the body weight and to the caloric value of the diet. The significant data for 14 patients are summarized in table 3.

The average total weight of average intake was 3176 grams (7 pounds) with a range from 2082 to 4860 grams. Intakes of these magnitudes form a very significant fraction of the total body weight. In fact, two patients had daily mass exchanges of 9.3 per cent and 9.5 per cent of their body weights respectively although the average for the series was 6.9 per cent of the body weights. Of the total intake, 61 per cent was food and 39 per cent water. Considerable variation in the proportions of

TABLE III
Relation of Intake to Caloric Value and Weight Gains

1	2	3	4	5	6	7	8	9	10	11	12	13
Patient	Total intake		Food intake			Food solids			Calories per gram			Wt Gain
	Weight	% Body weight	Weight	% Total intake	% Body weight	Weight	% Total intake	% Food intake	Total intake	Food intake	Food solids	Gms per day
	Gm	%	Gm	%	%	Gm	%	%	Cal	Cal	Cal	Gm
1	3345	7.0	1557	46	3.3	465	14	30	83	1.79	5.99	121
2	2082	9.3	1748	84	8.0	401	19	23	1.11	1.32	5.76	83
3	3102	7.4	1678	54	4.0	466	15	28	.92	1.70	6.12	248
4	2853	6.3	1927	68	2.3	529	18	27	1.12	1.66	6.05	157
5	2994	5.7	1303	43	2.5	382	13	29	.99	2.29	7.80	114
6	4311	8.5	2521	58	5.0	841	19	33	1.18	2.02	6.05	421
7	3141	6.7	2283	73	4.8	558	17	24	1.04	1.43	5.88	143
9	3722	7.6	2405	65	4.9	563	15	23	.92	1.43	6.09	164
10	2408	5.1	1791	74	3.8	500	20	28	1.33	1.79	6.40	154
14	3953	7.5	2140	54	4.1	506	13	23	.77	1.43	6.05	257
15	3091	6.2	1765	57	3.5	527	17	29	1.05	1.85	6.18	177
16	2771	4.9	1728	62	3.0	521	19	30	1.19	1.92	6.36	178
17	2837	5.9	1766	62	3.6	475	17	24	.99	1.58	5.89	131
18	4860	9.5	2700	56	5.3	776	16	29	.99	1.77	6.17	186
Ave	3176	6.9	1951	61	4.2	536	17	27	1.03	1.71	6.20	181

food and water are to be expected both in individuals and in the daily levels. For two patients, water formed 64 to 57 per cent of the total daily intake. In contrast, one patient drank only 16 per cent water. Conversely the weight of food varied from 43 to 84 per cent of the total intake. The food intakes ranged from 1300 to 2700 grams with an average of 1951 grams per day. These figures represent on the average 4.2 per cent of the respective body weights. Since the figures for food include the large quantities of water in the food substances, the total weights of the food solids have been estimated separately (column 7). It may be noted that 536 grams of solids were taken per day with a variation from 382 to 841 grams. The food solids correspond to 27 per cent of the total weight of food and to 17 per cent of the total weight of intake.

Since the foods taken, with a few exceptions, were general mixed varieties, it is important to note the relations which existed between total weight and energy content of the intake. As might be expected, the marked variability in extra water produces a great variation in the relation of total weight of intake to caloric value. Although the average figure is 1.03 calories per gram the extremes are 1.33 and .77 calories per gram. If the weight of only the food substances is considered the variability is reduced, the average becomes 1.71 calories

per gram. If, however, only the food solids are considered, there is a fair degree of constancy, about the average value 6.20 calories per gram. The only marked variation occurred in patient 5 who ate a diet containing 85 per cent of fat which produced 7.80 calories per gram of solids.

An attempt has been made to correlate these data pertaining to food weights with the observed changes in body weight. Although the average daily weight gain (181 grams) corresponds to 5.6 per cent of the total weight of intake per day, there is, as would be expected, little individual correspondence between these two series of observations, also with respect to the total weight of food intake, or conversely the total weight of water intake, no clear cut relation to weight gain is apparent. Finally the average weight gain corresponds to 3.4 per cent of the weight of the food solids but here again an examination of the data fails to reveal a true relation between weight of intake and body weight gain. It may therefore be stated that a permanent gain in body weight bears no relation to the total mass of material, either food or water, which is ingested.

If we accept the principle that the truly significant aspect of a fattening diet is its caloric value, the relation of the weight changes of these patients to their caloric intakes becomes of great interest. From table 1 it will be seen that the average caloric intake for 16 patients was 3320 calories with a range from 2310 to 5090 calories. However, in proportion to the sizes of the individuals, the variation appears to be much less. From table 4, column 13, it may be seen that the average calories per kilogram of average weight is 73, with a range from 57 to 105 calories per kilogram. Attention may be called to the fact that the patient having only 2310 total calories actually averaged 105 calories per kilogram. Ratios of this order of magnitude serve to emphasize the point that the standards of 30 to 40 calories per kilogram which are often encountered certainly are inadequate when one is dealing with underweight patients. Our ratios compare rather with those of Coleman and DuBois² who found 50 to 70 calories per kilogram necessary to maintain the weights of typhoid patients. If, however, the calories per kilogram are calculated on the basis of the ideal weights of the patients much lower figures are obtained. In this series of patients who increased from 26 per cent underweight to 16 per cent underweight, the average intake was 57 calories per kilogram of ideal weight in contrast to the 73 calories per kilogram average actual weight.

It may be accepted as a fact that a food intake adequate for weight gain exceeds that for maintenance. In order to obtain a measure of how much thin people actually eat regardless of their impressions, preliminary observations were made on eight patients. These patients were instructed to eat just as they did at home or just as they wished, although in most cases it was impossible for them to avoid an increase in intake as shown by their weight gains. These results are tabulated in table 4.

The average food intake was only 2060 calories or roughly two-thirds of the corrective diet. In proportion to body size, these intakes average 52

calories per kilogram actual weight In contrast it may be noted that these patients took in 68 to 71 calories per kilogram of average actual weight during the period of treatment These data show that according to certain standards, thin people do eat large quantities of food but again it may be stressed that the total caloric intake is small in these persons

The increase in the food capacity of our patients is shown in table 4, columns 7 to 11 Columns 8 and 11 record the calories per kilogram of actual weight eaten during the first and last weeks It at once appears that there is little difference between these figures The apparent discrepancy is due to the increase in final weight rather than to a lessened intake When the total calories taken during the first and last weeks are compared it will be noted that patients ate 400 more calories or 13 per cent more food than during the first week As a matter of fact this maximum intake was attained usually in the second or third week, an observation which supports our practice of starting a patient at once on a full diet or, at most, of making one or two steps at short intervals A comparison of the figures for the first week with those for the preliminary period shows that the patients who ate 2060 calories for maintenance averaged 2730 calories during the first week and reached 3160 calories in the last week of dieting These increases are 32 and 53 per cent respectively No significant difference in reaction could be noted in the patients having acute undernutrition as contrasted with chronic undernutrition

The changes in weight which have been produced by the above diets are recorded in table 5

TABLE V
Weight Increase

1	2	3	4	5	6	7	8	9
Patient	Weeks	Initial weight		Final weight		Increase weight		Rate of increase Grams per day
		Kilo	% Under weight	Kilo	% Under weight	Kilo	%	
1	13½	41.9	30	53.3	11	11.4	27	121
2	3	21.2	27	22.9	21	1.7	8	83
3	3	38.9	31	44.1	22	5.2	13	248
4	4	43.1	20	47.5	12	4.4	10	157
5	6	49.5	23	54.3	16	4.8	9	114
6	6	41.4	42	59.1	17	17.7	43	421
7	12	40.9	25	52.9	3	12.0	29	143
8	2	44.0	19	45.7	15	1.7	4	121
9	2	47.6	20	49.9	18	2.3	5	164
10	4	44.6	26	48.9	18	4.3	10	154
11	3	34.7	28	36.9	23	2.2	6	102
12	8	35.1	40	42.2	28	7.1	20	127
13	3	39.5	32	43.0	26	3.5	9	166
14	3	49.9	15	54.8	6	5.4	11	257
15	5	46.6	25	52.8	16	6.2	14	177
16	4	54.1	13	59.0	6	4.9	9	178
17	2½	46.7	18	49.0	14	2.3	5	131
18	7	46.4	30	55.5	17	9.1	19	186
Average	5	42.5	26	48.4	16	5.9	13	169

The 18 patients forming the entire series gained 106 2 kilograms, an average of 5 9 kilograms per person. The largest individual gain was 17 7 kilograms in six weeks, the smallest 1 7 kilograms in three weeks. The average increase in weight per day was 169 grams, with a range from 83 to 421 grams per day.

It is further of interest to note the relation of the weight increments to the body status which had existed previously. The patients increased their body mass on the average by 13 per cent varying from 4 per cent in two weeks to 43 per cent in six weeks. On the whole they changed stature at the rate of 2 8 per cent per week.

The six patients who were more than 30 per cent underweight appear to have gained 35 per cent more rapidly than the 10 who were less than 30 per cent underweight, 211 grams per day as contrasted with 156 grams per day (table 6).

TABLE VI
Weight Gain in Relation to Degree of Undernutrition

Less than 30 per cent					More than 30 per cent				
Patient	Wt gain per day	Caloric intake	Calories per kilo	Wt gain per 100 extra cal	Patient	Wt gain per day	Caloric intake	Calories per kilo	Wt gain per 100 extra cal
	Gm	Cal	Cal	Gm		Gm	Cal	Cal	Gm
2	83	2310	105	15	1	121	2790	59	20
4	157	3200	71	13	3	248	2850	69	29
5	111	2950	57	13	6	421	5090	101	17
7	113	3280	70	12	12	127	3310	85	9
9	164	3430	70	11	13	166	3150	83	11
10	151	3200	68	13	18	186	4790	94	9
11	257	3060	59	28					
15	177	3260	66	17					
16	178	3310	58	17					
17	131	2800	58	18					
Ave	156	3080	64	16	Ave	211	3710	82	16

It would appear, therefore, as if the rate of weight gain might vary inversely with the degree of undernutrition. This phenomenon is, however, apparent only. Although the rate of weight gain of the six grossly undernourished patients was high, this may be explained readily on the higher caloric intake. These patients averaged 3710 calories per day in contrast to 3080 for 10 other patients, or 82 calories per kilogram in contrast to 68 for the other group. Further confirmation of this point is obtained by comparing the grams weight increase per 100 extra calories in the two groups. The six grossly underweight patients averaged 16 grams per 100 extra calories as compared with 10 grams for the other subjects. Such a comparison of the weight change bears a direct relation to the

increase in food intake, it becomes important to attempt a statement of this relationship. More strictly speaking, the relationship exists between the rate of weight gain and the excess of food intake. A discussion of this energy balance requires a knowledge not only of the intake but of the output of energy. The total daily energy output could not be determined. We have used, however, three methods of approximating this information. The preliminary diets may be regarded as representative of the maintenance intake and the excess calories estimated by difference between intake on the high caloric and on the maintenance diets minus the extra specific dynamic action of the dietary increase. This calculation for seven patients on whom preliminary diet data are available appears in table 7.

TABLE VII
Extra Calories Estimated from Preliminary Diet

1	2	3	4	5	6	7	8
Patient	Caloric intake	Maintenance calories	Gross extra calories	Increase S D A	Net extra calories	Weight gain per day	Weight gain per 100 extra cal
	Cal	Cal	Cal	Cal	Cal	Gm	Gm
2	2310	1880	430	40	390	83	21
3	2850	1670	1180	120	1060	248	23
4	3200	2270	930	90	840	157	19
13	3450	2220	1230	120	1110	166	15
15	3260	2340	920	90	830	177	21
16	3310	2450	860	90	770	178	23
17	2800	1770	1030	100	930	131	14
Ave	3030	2090	940	90	850		19

It may be noted that these patients ingested 3030 calories per day in contrast to 2090 calories during the preliminary period. If we neglect the slight weight increase during the earlier period, 940 extra calories were eaten. The specific dynamic action of this extra food reduces the net extra calories to 850. If the respective daily weight gains are divided by the net extra calories it is found that these patients gained 19 grams per 100 extra calories eaten.

A second approximation of the total energy output is obtained by the arbitrary assumption that the extra basal heat production is 20 per cent of the basal level. The total heat output is, therefore, Basal + 20 per cent + specific dynamic action (10 per cent of the food intake). The details of this method are not given but the average for 16 patients is 13 grams per hundred extra calories.

The third method resembles the second except for the arbitrary assumption of 500 calories as the extra basal heat output. The energy output is, therefore, Basal + 500 calories + specific dynamic action (10 per cent of

intake) The application of this calculation to the data of 16 patients appears in table 8

The gross intake of the 16 patients averaged 3320 The average figure obtained by adding the observed 24 hour basal metabolism, 10 per cent of the gross food intake for specific dynamic action, and 500 extra basal calories is

TABLE VIII
Extra Calories Estimated from Basal Metabolism

1	2	3	4	5	6	7	8
Patient	Caloric intake	Caloric output			Extra calories	Weight gain per day	Weight gain per 100 extra cal
		Basal	SDA	Total			
	Cal	Cal	Cal	Cal	Cal	Gm	Gm
1	2790	1400	280	2180	610	121	20
2	2310	1020	230	1750	560	83	15
3	2850	1200	290	1990	860	248	29
4	3200	1190	320	2010	1190	157	13
5	2980	1280	300	2080	900	114	13
6	5090	1670	510	2680	2410	421	17
7	3280	1300	330	2130	1150	143	12
9	3430	1150	340	1990	1440	164	11
10	3200	1170	320	1990	1210	154	13
12	3310	1080	330	1910	1400	127	9
13	3450	1070	350	1920	1530	166	11
14	3060	1350	310	2160	900	257	28
15	3260	1410	330	2240	1020	177	17
16	3310	1410	330	2240	1070	178	17
17	2800	1310	280	2090	710	131	18
18	1790	1830	180	2810	1980	186	9
Ave	3320			2140	1180		16

Nitrogen storage figures were available on only ten of these patients. If the weight gain per day for these patients is distributed into protein and fat, it will be found that the average weight of fat deposited per 100 extra, non-protein calories is 11.7 grams. This figure may be compared with the theoretical 12.6 grams of fat tissue per 100 extra fat calories.

2140 The net extra calories eaten are, therefore, 1180. The average of the respective weight gains divided by the extra calories is 16 grams per 100 extra calories.

Since in all probability no one of these methods of estimation exactly expresses the facts in any given patient, the most reasonable estimate is obtained by averaging the results of the three methods. The average figure, 16 grams per 100 extra calories, may be regarded as fairly representative of the rates at which our patients were observed to gain weight. This method of expression, in our opinion, provides a more accurate picture of the average rate of the phenomenon of weight gain than any other form of expression. The expression of weight changes in terms of total gain or of percentage increase is not so satisfactory, because the end result, which have been ob-

tained. The mechanism by which these results are obtained is suggested by our observation of a fair degree of uniformity of the figures for weight change per 100 extra calories which is often in marked contrast to an apparently slow or rapid alteration in weight.

Further emphasis regarding the fundamental significance of these data is obtained by comparing the observed figures for grams weight gain per 100 extra calories with what is theoretically probable. In the estimation of the weight increase which might be expected from each extra 100 calories, it is necessary to keep in mind the nature of the tissues deposited. Mitchell and Carman⁴ have shown the great variations in the several tissues which occur in animals on very similar diets. Also the great variation in water content of tissues is well known. However, admitting the inherent inaccuracies of the calculation, an approximation has been made on the assumption that the tissues deposited were protein and fat containing 75 per cent and 15 per cent water respectively.

Ten of the 16 patients had an average positive nitrogen balance of 2.3 grams.⁷ It is, therefore, assumed that 2.0 grams nitrogen were stored by the average patient. If we refer to the three calculations above, the 2 grams of nitrogen were stored simultaneously with 900, 1200 or 1400 calories respectively. In each instance 2 grams of nitrogen correspond to 50 calories and to 50 grams of protein tissue. The fatty tissue estimates which correspond to the above total calories would be 107, 145, and 170 grams respectively. Per 100 extra calories, therefore, the theoretical weight gain in each instance would be 17.4, 16.3, 15.7 grams respectively with the average of 16 grams per 100 extra calories. In view of the several assumptions which have been made, too much stress should not be laid upon the coincidence of this close approximation of the observed and the theoretical weight gains. It is felt, however, that an agreement of this order provides considerable evidence in favor of the thesis that weight gain is regulated by the maintenance of an energy intake in excess of energy output and the rate of gain is determined by the magnitude of this excess intake.

CONCLUSIONS

1. An analysis of the diets taken by 16 patients who were being treated for undernutrition showed an average caloric intake of 3320 calories per day.

2. 7.7 per cent of the calories were supplied by protein, 27.5 per cent by carbohydrate and 64.7 per cent by fat.

3. The majority of the diets had ketogenic and anti-ketogenic ratios of 57 to 83, although the upper limit which was used was 3.17.

4. The estimation of the acid-base balance of the diets suggests that the average menus supplied a marked preponderance of basic radicles.

5. The total weight of intake averaged 3180 grams per day of which 61 per cent was food and 17 per cent food solids. No relation was observed between the weights of several intakes and the rate of weight gain.

6. The caloric intakes which were necessary for rapid weight gain averaged 73 calories per kilogram of actual weight, or 57 calories per kilogram of ideal weight.

7. Thin people eat small quantities of food per day in spite of the apparent high levels which result from certain forms of calculation.

8. The food capacity of patients altered rapidly to permit the ingestion of 30 to 50 per cent increases of food intake.

9. Eighteen patients gained 10 to 24 kilograms in five weeks. The average rate of weight gain was 160 kilograms per day.

10. Dependent upon an approximation of the total caloric output, the extra calories ingested per day have been calculated. The rates of weight gain which were observed averaged 10 grams increase in body weight per 100 extra calories. This observed value is within reasonable agreement with the corresponding theoretical value.

BIBLIOGRAPHY

1. ATWATER, W. C., and BRYANT, A. P. The chemical composition of American food products, U. S. Dept. of Agriculture, Bull. No. 28, 1906, p. 19.
2. COLEMAN, W., and DeBORS, F. F. The influence of the high caloric diet on the respiratory exchanges in typhoid fever, *Arch. Int. Med.*, 1911, xiv, 162-200.
3. GRIEDENSWALD, J., and RICHMAN, J. Diet in health and disease, 1926, W. B. Saunders Co., Philadelphia.
4. MITCHELL, H. H., and CARMAN, G. G. The composition of the gains in weight and the utilization of food energy in growing rats, *Am. Jr. Physiol.*, 1925, lxxvi, 395-410.
5. SHERMAN, H. C. Food products, 1921, The Macmillan Co., New York.
6. STRANG, J. M., and EVANS, F. A. Undernutrition and its treatment by adequate diet. *ANN. INT. MED.*, 1933, vii, 45-63.
7. STRANG, J. M., McCILGAGH, H. B., and BROWNE, M. A. Nitrogen metabolism during the dietary correction of undernutrition. (In press.)
8. WATKIN, D. S. Nutritive value of food materials, Univ. of Mich. Hosp., 1928.

THE RHEUMATIC LUNG *

By C P HOWARD, B A , M D , F R C P (Canada), *Montreal, Canada*

THE APPRECIATION that the rheumatic virus may in certain cases attack both lung and pleura dates back almost two hundred years. Thus Boerhaave,¹ in 1737, stated that rheumatism invades "sometimes the brain, lungs and bowels." Storck² in 1762 also recognized the pleurisy of rheumatism. Maximilian Stoll³ in 1788 was, however, the first to speak of "rheumatic pleurisy" and "rheumatic peripneumonia," but like Boerhaave gave no pathological description of these lesions. Chomel⁴ in 1813 spoke with great caution of the inflammation of the pleura or lung which follows rheumatism. Latham⁵ in 1845 and Fuller⁶ in 1854 fearlessly championed the conception of a rheumatic pneumonia. Latham reported an incidence, of pulmonary affections in 136 cases of rheumatic fever, of 17.0 per cent. Fuller's series of 241 cases of acute rheumatism revealed pulmonary lesions in 41 cases or 17 per cent, these like Latham's figures were clinical observations. However, Fuller also reported 16 postmortems in which a pneumonia was found only twice, pleurisy five times, and bronchitis once. This discrepancy between clinical and postmortem incidence, I fear, still holds true today. In an excellent article by my father, the late R. P. Howard⁷ in Pepper's *System of Medicine* in 1885, a good deal of space is devoted to the incidence of rheumatic pleurisy and pneumonia. According to this article, pulmonary and pleural manifestations occurred,

in rheumatic endocarditis in only 10.5 per cent
in rheumatic pericarditis in 58 per cent
in rheumatic endopericarditis in 71 per cent.

figures which are suggestive in themselves.

Cheadle⁸ in 1889 also speaks of a pleurisy in rheumatic fever which may occur in two distinct ways. First it appears frequently toward the end of rheumatic heart disease, partly as a result of mechanical congestion of the pleura caused by the valvular defect or by pericarditis or by extension from the latter. Secondly as an initial phenomenon, preceding, accompanying, or immediately following the arthritis. Cheadle even suggests that it may occur quite independently of all other rheumatic infections. He reports two cases of pleuropneumonia in children but without postmortem confirmation.

Steven Mackenzie,⁹ in a later contribution, found that among 3433 cases of rheumatic fever, pleurisy or pneumonia occurred in 9.94 per cent. In Germany, according to Pribram¹¹ in 1899 among 627 cases of rheumatic fever, there were four with a pneumonia, three of these were associated with endopericarditis and one with endocarditis alone, three had a pleurisy in addition. Only one case was studied post mortem and in it there was a

* Read before The American College of Physicians Montreal February 8 1933

bilateral lobular pneumonia In other words, Pribram found an incidence in this German series of 0.64 per cent as compared with an average incidence, according to the British reports, of 1.52 per cent

In 1903 Thomas McCrae¹² reported from the Johns Hopkins Hospital, four pulmonary complications among 270 rheumatic fever patients, an incidence of 1.5 per cent, three of these were pleurisy and one a pneumonia

RHEUMATIC PLEURISY

According to Homer Swift,¹³ in his article in Nelson's Loose-Leaf Medicine, 1920, the incidence of pleurisy is variously reported as from 2 to 20 per cent W S Thayer¹⁴ found in a series of 25 postmortems on acute rheumatic heart disease, a sero-fibrinous pleurisy in 10 cases (40 per cent) and a chronic adhesive pleurisy once In a study by the writer and Dr E S Mills,¹⁵ of 241 cases of rheumatic fever or its sequellae occurring in a three year period (1925-1927 inclusive), there were seven cases of pleurisy among the 96 cases in the acute arthritic stage (an incidence of 7.3 per cent) and 20 cases in association with 130 cases of endocarditis, pericarditis, chorea or other rheumatic manifestations (an incidence of 13.3 per cent) The seven cases in the acute arthritic stage were sero-fibrinous and of these, three were bilateral, two right-sided, and two left-sided Among the 20 cases in the other group, five were acute sero-fibrinous and 15 were chronic adhesive or obliterative pleuritis In short, in 226 individual patients there was a pleurisy of some type in 27, an incidence of 11.9 per cent There was an acute fibrinous pleurisy in four, sero-fibrinous in 12 and a chronic fibrous or obliterative pleurisy in eleven It was right-sided in seven, left-sided in 10 and bilateral in 10 cases

It is generally agreed that pleurisy is, next to carditis, the most common complication of rheumatic fever Our conception of rheumatic pleurisy is that of a specific inflammatory lesion, similar to that of a rheumatic pericarditis or arthritis Although this view has long been accepted, no definite description or characteristic pathological picture appeared in the earlier writings It is true that in 1882 Longstreth,¹⁶ of the Pennsylvania Hospital, emphasized the marked fibrinous character of the exudate and that Bezancon and Weil¹⁷ in 1926 recorded the predominance of endothelial cells in the exudate It was not, however, until 1928 that Paul¹⁸ first described the specific nature of the pleurisy On close inspection there is a thin film of fibrin on the surface of the pleura in the earliest stage, which may be replaced later by a thick fibrinous exudate on both parietal and visceral pleurae Subsequently organization of the fibrinous adhesions occurs Paul never found, however, the thickened hyalinized pleura seen so frequently in the late stages of tuberculosis

Histologically the lesion resembles that seen in rheumatic pericarditis " It is characterized primarily by changes in the pleural endothelium causing metaplasia and eventual death and desquamation of the endothelial cells This is accompanied by a characteristic type of severe, chronic, non-suppara-

tive inflammatory reaction throughout the subpleural layers" Paul makes no mention of any structure remotely resembling the Aschoff body. This specific form of pleuritis is undoubtedly a common manifestation of the serous membrane involvement of the active stages of the disease and it is much more frequent than the pulmonary lesion proper. We agree with Gouley and Eiman³⁰ that it was often responsible for the diagnosis of so-called rheumatic pneumonia by the earlier students of the disease, as Latham and Fuller, who interpreted the physical signs of compression of the lung parenchyma by the pleural exudate as pneumonia and consequently reported an unusually high incidence of the latter. A pleurisy is found in the majority of cases that come to autopsy in either the acute or the subacute stage of rheumatic fever. It may be most extensive when complicating a widespread mediastinitis and pericarditis and is then usually associated with an effusion. However, it may exist in small isolated patches of fibrinous exudate seen more commonly over the lower lobes but at times also over the upper ones. Such small patches, of course, are not recognizable by any method of physical examination.

Rolly's³¹ series of 3620 cases of acute rheumatic fever yielded 88 cases of pleurisy, or an incidence of 2.5 per cent, and in half of these the pericardium was also involved. While for many years the opinion had been expressed that the pericardium was first infected and the pleura only by direct extension, Paul concluded, in accord with the more recent conception of the widespread distribution of the rheumatic vascular lesions throughout the body, involving the peripheral arteries and arterioles, that the pleural lesions are part of the generalized process and not the result of a direct extension from the pericardium. Our pathologist, Dr. L. J. Rhea, has demonstrated in the pleura of one of our cases, Aschoff-like bodies.

VASCULAR LESIONS

Since the description of Coombs,²⁰ Klotz,²¹ and Pappenheimer and von Glahn²² of the histological changes in the aorta in rheumatic fever, the peripheral blood vessels, including those of the lung, kidney, pancreas, colon, etc., have been also carefully studied. In a subsequent paper, von Glahn and Pappenheimer²³ reported that in the lungs of two of their cases practically every small branch of the pulmonary arteries was involved. Paul²⁴ found in one case typical Aschoff bodies in the adventitial layers of the pulmonary arteries as well as in those of the aorta. The gross and histological changes are not so striking in the pulmonary arteries of moderate size. In the small arterioles of the lungs, Paul found in from 20 to 40 per cent of the active rheumatic subjects a periarteritis in which all the coats were involved, though the intima and the adventitia were most affected. It is a striking fact, as pointed out by Paul, that in the vessels as in the pleura it is the endothelium which seems to be primarily involved and that this endothelial lesion is associated with a characteristic type of subendothelial perivascular and even interstitial reaction. Paul believes that there is a relationship be-

tween this type of lesion and the well known Aschoff body of the myocardium

RHEUMATIC PNEUMONIA

No one will deny that a lobar pneumonia due to various types of pneumococci may occur during the course of rheumatic fever, but the question arises, is there a specific rheumatic pneumonia? Besnier (quoted by Garrod²⁵) regarded the lesion in the lung as "splenization," and not a true exudative process but rather an intense hyperemia and edema with collapse and atelectasis. Coombs also considered atelectasis and passive congestion as responsible for the production of the pulmonary signs, but does admit of the possibility of a consolidation appearing in the right upper lobe, an area relatively immune to the influence of cardiac failure. Garrod has denied the existence of a specific pneumonia. Thayer found in 50 per cent of 25 fatal cases of rheumatic fever a terminal pneumonia or bronchopneumonia.

Rabinowitz²⁶ believed that a specific pneumopathy does occur and is clinically distinguishable from lobar as well as bronchopneumonia but that the ultimate proof of the existence of Aschoff bodies in the lung had not yet been produced. Paul found in the lungs of more than 50 per cent of 30 cases, "evidences of a focal hemorrhagic lesion, rather widespread, involving individual lobules or group of lobules, which might be interpreted as an early or hemorrhagic stage of a broncho- or lobular pneumonia." He, however, did not feel that sufficient evidence had been obtained to prove that this focal hemorrhagic lesion was a *specific* manifestation of rheumatic fever, although it seemed a fairly characteristic finding.

Naish²⁷ studied the consolidation in the lungs of six cases of rheumatic fever which had died at the height of the disease. He was struck in the first place with the extent of the pulmonary consolidation in four of the six cases, as nearly all of the five lobes were involved. Secondly, he emphasized the peculiar india-rubber like consistency of the affected lung; it was very tough and non-friable on section. The color too was striking, as the cut surface was of a purplish red shade, quite homogeneous, and showing none of the granite or marbled appearance of other pneumonias. Microscopically the most striking feature was the enormous endothelial proliferation, the cells apparently originating from the walls of the alveolar capillaries. Multinuclear cells were fairly frequent. These cells were mixed with a few fibroblasts and polymorphonuclear leukocytes. The reactive process appeared to be identical with that described by Aschoff and Tawara and Coombs as pathognomonic of rheumatic infection elsewhere in the body.

Coburn²⁸ found, among 3000 rheumatic subjects at the Presbyterian Hospital, New York, 30 patients in whom there suddenly developed pulmonary solidification accompanying active rheumatic disease without evidence of congestive heart failure.

The rapid disappearance and the migratory nature of these areas of consolidation were characteristic. He does not, however, describe anything characteristic in the postmortem appearance of the lungs other than

to mention as present, congestion, edema and a hyalinized membrane lying against the alveolar walls and some polymorphonuclear infiltration. He confesses that "the histological lesions regarded as specific in rheumatic disease have not been defined in the lung."

Eiman and Gouley,²⁹ as well as Naish, have described lesions in the lung that were eventually considered characteristic of the rheumatic virus, as seen elsewhere in the body. In an elaborate study in 1932 of nine fatal cases of acute rheumatic fever, Gouley and Eiman attempt to describe this specific pneumopathy. The inflammatory pulmonary reaction consisted of an interstitial exudate of large endothelial cells, identical in morphology with those found in the rheumatic heart lesions and generally considered pathognomonic of rheumatic fever. Hemorrhage and fibrinous exudate were prominent features. Both lungs were moderately enlarged and bulky and did not collapse; the lower lobes were solid and deep blue. On section the tissue was dark red in color and presented a cut surface of unusually smooth appearance and also a fairly dry one, giving a liver-like appearance resembling somewhat atelectasis. The histologic study revealed an acute interstitial inflammatory process, characterized by hyperemia, edema, and perivascular infiltration of large endothelioid cells, as well as multinuclear giant cells, plasma cells, lymphocytes and but relatively few polymorphonuclear leukocytes.

According to these writers, "The acute pulmonary lesion of rheumatic fever, rheumatic pneumonia, or pneumonitis, is an acute interstitial inflammation, having as its basis the vascular damage and perivascular infiltration that are common to all rheumatic lesions." "The rheumatic lesion's color, varying from dark blue to a rusty brown, and the delicate white tracing under the pleura, due to interstitial exudate, and its appearance on section are distinct features." "The dark red, firm, finely granular, slightly moist cut surface, doubtless led to its description as a splenization." Naish points out its resemblance to solid india-rubber. "It is not atelectasis." "Basal collapse, sometimes to an unusual degree and often accompanied by gelatinous edematous pleural adhesions, is seen frequently in subacute aspects of the disease." This consolidation could possibly be termed "perivascular pneumonia."

Histological examination gives definite proof of the identity of the lesion. The areas of acute involvement containing small perivascular groups of broken-up polymorphonuclears and slender irregular epithelioid cells might conceivably be the first of a number of phases of inflammatory reaction and be followed later by a non-proliferative process, the Aschoff "nodule." It is this interstitial perivascular infiltration of large cells, often multinucleated, that is a significant part of the histologic picture in rheumatic pneumonitis.

A third phase of the reaction is suggested by the presence of fairly large cells with solid irregular nuclei replacing the large Aschoff cells and giving the impression that such a lesion is a subacute one, verging on early sclerosis.

Another important feature is the vascular destruction that he myo- seen in rheumatism, the endothelial hyperplasia, the rupture of ca₁ with hemorrhage and the liberation of fibrin. Eight of the nine ca₁ Gouley and Eiman exhibited a pericarditis and all nine had some a₁₀- manifestations of cardiac rheumatism.

In the Montreal General Hospital during an eight year period a pneumonia was recognized clinically nine times in 489 rheumatic subjects, however, only two of these nine cases came to autopsy but in both the histological study was characteristic of a specific pneumonitis.

A clinical picture of lobar pneumonia may appear about the same time as the acute cardiac manifestations of rheumatic fever. However, it does not follow the presence of an upper respiratory infection as is usually the case in bronchopneumonia, nor does it present the striking features of the classical picture of lobar pneumonia, namely chill, high fever, rusty sputum, severe pleural pain, and tachypnea. Its symptoms are much less spectacular there is no chill cough may not be troublesome the sputum is scanty and tenacious and only occasionally is it blood streaked bacteriologically the sputum does not contain virulent pneumococci as for the fever, it runs an irregular course, varying from 102 to 105 degrees and there is but a slight elevation of the respiratory rate.

The physical signs are much more striking than the symptoms. There may be dullness to percussion and bronchial breath sounds over the lower, or even over the upper lobes. But the striking feature is the transient character of the physical signs which may be present for only two to four days, though in some cases they may be prolonged to a week or more. The signs may recur in the same area in a few weeks.

The signs of consolidation may be replaced by flatness and absence of breath sounds due to a massive pulmonary collapse or to a pleural effusion, which may persist for weeks. There may be no râles present during the stage of consolidation or if present they are not as numerous or as intense as in the frank lobar pneumonia. In the later stage, large, coarse pleuritic râles may be heard due to the associated fibrinous pleurisy.

BIBLIOGRAPHY

- 1 BOERHAAVE, H. Aphorismi de cognoscendis et curandis morbis, Editio Leydensis quinta auctior, Lugundi Batavorum, 1737.
- 2 STORCK, A. De Febre arthritica et Rheumatica, etc., Editio altera, Vindobonae, 1762, II, 119.
- 3 STOLL, M. Rationis Medendi, Viennae, 1788.
- 4 CHOMEL, A. F. Essai sur le Rheumatisme, Paris, 1813.
- 5 LATHAM, P. M. Lectures on subjects connected with clinical medicine comprising diseases of the heart, 1845-1846, edited by Robert Martin, London, Lect. 18, 1876.
- 6 FLUHR, H. W. On rheumatism, rheumatic gout and sciatica, their pathology, symptoms and treatment, 1854, New York.
- 7 HOWARD, R. P. Acute articular rheumatism. PEPPER, W. System of medicine, 1885, II 12-59.
- 8 MACFARLANE, S. An address on some points regarding acute rheumatism requiring investigation, Brit. Med. Jr., 1886, I, 99.

- 9 CHEADLE, W B Clinical lecture on an outbreak of rheumatic pneumonia, *Lancet*, 1888, i, 861
- 10 CHEADLE, W B The various manifestations of the rheumatic state as exemplified in childhood and early life, 1889, Smith, Elder and Co, London, pp 1-127
- 11 PRIBRAM, A Der Akute Gelenkrheumatismus Pneumonie NOTHNAGEL, C W H *Spec Path u Therap*, 1899, A Holder, Wien, p 172
- 12 McCRAF, T Acute articular rheumatism, *Jr Am Med Assoc*, 1903, xi, 211-216
- 13 SWIFT, H F Complications of rheumatic fever NELSON'S Loose-Leaf Med, 1920, i, 418-420
- 14 THAYER, W S Notes on acute rheumatic disease of the heart, *Bull Johns Hopkins Hosp*, 1925, xxxvi, 102
- 15 HOWARD, C P, and MILLS, E S Acute articular rheumatism and other members of the rheumatic cycle, *Canadian Med Assoc Jr*, 1928, xix, 403
- 16 LONGSTRETH, M Rheumatism, gout and some allied disorders, 1882, F and W Wood, New York, p 133
- 17 BEZANCON, F, and WEIL, M P La Cortico-Pleurite Rheumatismale, *Ann de Méd*, 1926, xix, 184
- 18 PAUL, J R Pleural and pulmonary lesions in rheumatic fever, *Medicine*, 1928, i, 383
- 19 ROLEY, F Der akute Gelenkrheumatismus, 1920, Berlin
- 20 COOMBS, C F Rheumatic heart disease, 1924, John Wright and Sons, Bristol, pp 203, 258
- 21 KLOTZ, O Rheumatic fever and the arteries, *Trans Assoc Am Phys*, 1912, xxvii, 181
- 22 PAPPENHEIMER, A M, and VON GLAHN, W C Lesions of the aorta associated with acute rheumatic fever and chronic cardiac disease of rheumatic origin, *Jr Med Res*, 1924, xlv, 489
- 23 VON GLAHN, W C, and PAPPENHEIMER, A M Specific lesions of peripheral blood vessels in rheumatism, *Am Jr Path*, 1926, ii, 235
- 24 PAUL, J R Lesions in the pulmonary artery in rheumatism, *Arch Path*, 1927, iii, 352
- 25 GARROD, A E A treatise on rheumatism and rheumatoid arthritis, 1890, London
- 26 RABINOWITZ, M A Rheumatic pneumonia, *Jr Am Med Assoc*, 1926, lxxxvii, 142-144
- 27 NAISH, A E The rheumatic lung, *Lancet*, 1928, ii, 10
- 28 COBURN, A F The factor of infection in the rheumatic state, 1931, Williams and Wilkins Co, Baltimore, p 35
- 29 EIMAN, J, and GOULEY, B A Rheumatic pneumonitis, *Arch Path*, 1928, v, 558
- 30 GARDNER, B A, and FRANK, J The pathology of rheumatic pneumonia, *Am Jr Med*, 1928, vi, 100
- 31 SWIFT, H F The respiratory system (in article on rheumatic fever) NELSON'S Loose-Leaf Medicine, 1932, i, 429

TREATMENT OF POLYCYTHEMIA

THE RETICULOCYTE RESPONSE TO VENESECTION, PHENYLHYDRAZIN AND RADIATION *

By ERNEST H FALCONER, M D , F A C P , *San Francisco, California*

VENESECTION was formerly frequently employed as a therapeutic measure in the treatment of polycythemia, but its results have not been systematically studied. It has usually been considered as a measure of expediency rather than one of real value in the treatment of this condition. One of the present common objections to its use is based on the premise that repeated bleeding stimulates the bone marrow excessively, tending to premature exhaustion.

It was to test the validity of this premise, as applied to polycythemia vera, that this study was undertaken. The administration of phenylhydrazin hydrochloride by mouth, or radiation over spleen and long bones, has gradually replaced venesection as a method of reducing the red cells and hemoglobin in polycythemia vera. For this reason, the effects of these three methods of treatment on the bone marrow have been studied to yield a basis for comparisons. In addition, these same observations were extended to other types of polycythemia, giving a further basis for comparison.

The bone marrow reactions to phenylhydrazin in the treatment of polycythemia, have been studied and recorded by several observers and data are available in the literature ^{1, 2, 3, 4, 5}. No references were found recording the effects of venesection on the bone marrow in polycythemic states, nor were any observations found on the reticulocyte response to roentgen-ray treatment of polycythemia.

TERMINOLOGY

Polycythemia vera is used to designate the syndrome known as Vaquez-Osler disease, or erythremia. This syndrome is an absolute polycythemia with a palpable spleen and no definite lesions of the heart or lungs. There is no demonstrable cause for the high hemoglobin and red cell level. Polycythemia or erythrocytosis refers to an increased red cell and hemoglobin level secondary to pulmonary or cardiac disease, or some other definite lesion accounting for the abnormal red cell formation.

Polycythemia hypertonica refers to the syndrome described by Geisbock ⁶. It occurs in individuals with hypertension and arteriosclerosis, who show an erythrocytosis with or without an enlarged spleen. The condition may disappear or it may be quite similar in its course to polycythemia vera. It is probable that some of these cases are really polycythemia vera. Where the

* Read before the American College of Physicians, Montreal, February 7, 1933

From the Department of Medicine, University of California Medical School, San Francisco. This research was made possible by a grant from the Christine Breon Fund Income

term radiation is used it refers to roentgen-ray as no radium or other type of radiant energy was used

METHOD AND TECHNIC

The method of procedure in these studies was to use as an index of bone marrow function the reticulocyte count. This method is our nearest approach to a direct measure of marrow activity. It is well known in connection with the work of Minot and Murphy,⁷ in treating pernicious anemia by whole liver and liver fractions. The normal reticulocyte per cent is usually given as between 0.4 and 1.5.

The fluctuations in the percentage of reticulocytes in the peripheral blood have been tabulated with the hemoglobin and formed elements of the blood, as the different methods of treatment were carried out. It should be stressed that the main objective of these studies is to observe and record the reticulocyte per cent, as an index of bone marrow reaction to the different forms of treatment employed.

The blood counts were made, more than one hour after meals, with pipettes certified by the U. S. Bureau of Standards. Neubauer counting-chambers were used. Hemoglobin estimations were made on the Sahli instrument calibrated so that 13.7 gm. equal 100 per cent hemoglobin. Blood smears were stained by the Jenner-Giemsa method and reticulated counts were made on cover slips prepared with a film of cresyl blue counter-stained by Jenner-Giemsa stains, according to the method of Cunningham.⁸ All of the reticulated cell counts were checked by the author and the percentage was estimated by counting the number of reticulated cells per one thousand erythrocytes.

The majority of the venesections were performed by inserting a large caliber needle in the median basilic vein and allowing the blood to flow into an open vessel. The most satisfactory method was the use of a Vincent transfusion tube attached to the needle, negative pressure being induced by a rubber bulb fixed to the top of the tube. If everything is in readiness the actual bleeding requires about 15 minutes.

The roentgen-ray exposures were as follows: *

CASE NUMBER 1

<i>Dates</i>	<i>Treatments</i>
Nov. 17, 1932 to Nov. 21, 1932	Four exposures to spleen, anterior and posterior, alternating. Patient received 400 r measured in air (assumed to be 50 per cent SED) †
Dec. 7, 1932 to Jan. 5, 1933	Twelve treatments over long bones, tibiae, fibulae, radius, ulnae, humeri, femora. Dose 160 to 200 r measured in air. <i>Set-up 200 KV constant potential. Skin target distance 60 cm filtered through 5 mm copper plus 1 mm aluminum.</i>

* Roentgen-ray treatments were given under the direction of Dr. Robert S. Stone in charge of the Department of Roentgenology, University of California Hospital.

† Skin Erythema Dose

CASE NUMBER 2

Dates	Treatments
Oct 6, 1932 to Oct 21, 1932	Seven exposures to spleen anterior and posterior, alternating Patient received 200 r measured in air (assumed to be 25 per cent SED) †
Oct 25, 1932 to Nov 15, 1932	Four treatments over chest anterior and posterior, alternating—dose 200 r
Dec 6, 1932 to Dec 13, 1932	Four treatments over long bones, tibiae, fibulae, radii, ulnae, humeri, femora Dose 108 r measured in air (assumed to be 15 per cent SED) † <i>Set-up 200 KV constant potential Skin target distance 50 cm filter 5 mm copper plus 1 mm aluminum</i>

CASE NUMBER 3

Dates	Treatments
Sept 26, 1932 to Sept 27, 1932	Two exposures to spleen anterior and posterior Patient received 400 r measured in air (assumed to be 50 per cent SED)
Nov 4, 1932 to Nov 9, 1932	Four treatments over spleen anterior and posterior, alternating Patient received 400 r measured in air (assumed to be 50 per cent SED)
Dec 5, 1932 to Dec 8, 1932	Four treatments over long bones, tibiae, fibulae, radii, ulnae, humeri, femora Patient received 160 r (20 per cent SED) <i>Set-up 200 KV constant potential Skin target distance 60 cm filter 5 mm copper plus 1 mm aluminum</i>

MATERIAL

In order to secure an idea of the normal daily variation in the reticulocyte count, a graph of daily estimations was secured from counts on the author, a normal individual from the hematological standpoint

Normal Daily Variation of the Reticulocyte Count in Author

	Hgb	R B C	W B C	Retics	P M N	E	B Lymph	Mo-nos	Plate-lets		
12 27 32	90	4,740,000	7,050	0 2	53	16* 37†	2	2	36	7	290,000
12 28 32	87	4,910,000	4,350	0 0	54	18 36	3		38	5	330,000
12 29 32	84	4,870,000	5,100	0 5	59	16 43	4		29	8	240,000
12 30 32	85	4,750,000	6,900	0 6	61	20 41	2		29	8	270,000
12 31 32	92	4,890,000	5,400	0 2	60	22 38	5	1	22	12	330,000
1 1 33	95	4,650,000	9,800	0 9	55	9 46	9		25	11	
1 2 33	95	4,490,000	7,600	1 3	56	22 34	1	1	36	6	
1 3 33	95	4,910,000	7,250	0 9	54	14 40	2		35	9	
1 4 33	102	5,320,000	10,200	0 9	62	20 42	3		29	6	370,000
1 5 33	95	5,130,000	10,350	1 5	62	16 46	2		22	14	370,000
1 6 33	98	5,460,000	10,550	1 0	68	20 48	5		18	9	290,000
1 7 33	95	4,790,000	9,350	1 2	57	20 37		1	30	12	340,000
1 11 33	91	4,840,000	7,200	1 0	57	17 40	2	1	34	6	220,000
1 14 33	89	4 880,000	7,500	1 8	54	19 35	9		30	7	
1 17 33	85	5,010,000	9,100	1 0	52	10 42	1	1	32	14	270,000

Note In the P M N the number of neutrophils are divided into non-filament above (*) and filament below (†)

Four patients with polycythemia were studied

CASE I

A female patient, aet 54, married, no children, who first came under observation at aet 38 years. Her clinical and laboratory findings were reported in detail by Hurwitz and Falconer⁹ in 1918.

The diagnosis of polycythemia vera was made on the following findings: marked acro-cyanosis, palpable liver, and enlarged palpable spleen, absence of pulmonary and cardiac symptoms and abnormal physical findings, a long remission of over ten years, following benzol by mouth and roentgen-ray over the spleen.

Laboratory data October 11, 1916: hemoglobin 128 (Fleischl), red blood cells 10,064,000, white blood cells 9800, neutrophils 69, eosinophils 0, lymphocytes 21, monocytes 8, myelocytes 2. Viscosity (Hess Viscosometer) 77 (normal 45). Prothrombin determination normal. Electrocardiogram: heart within normal limits. Blood non-protein-nitrogen 43.9 mg, urea nitrogen 14 mg. Urine: amber, acid, specific gravity 1.020, albumin 0, sugar 0, casts 0, cells—few epithelial.

This patient, according to her history, is now in the nineteenth year of her disease. She has responded well to the following treatments:

Venesection (1915), benzol and radiation (1916)⁸, phenylhydrazin (1929–1930), roentgen-ray over the spleen (1928), venesection (1931), roentgen-ray over spleen and long bones (1932), phenylhydrazin (1932).

The disease for the past eighteen months has been pursuing the course of a mild polycythemia with few symptoms. As we have data extending over several years, a good base line has been established. For these reasons she was selected as a suitable patient to compare the effects of venesection, phenylhydrazin and radiation on the bone marrow, as evidenced by the reticulocyte response.

She was treated first by venesection until the red cell count fell to 4.64 million, hemoglobin 75 per cent. Treatment was now stopped and the red cell count was allowed to return to the pre-venesection level. Next she was given acetyl phenylhydrazin 0.1 gm daily for 14 days, the red cells again being allowed gradually to return to pre-treatment level. The same procedure was followed out with radiation by roentgen-ray.

CASE II

A Polish Jew, aet 45, divorced. First seen August 25, 1932, complaining of dyspnea, abdominal pains and headache. He gave a history of having polycythemia for the past nine years. For about five years he was under the care of a physician in New York City. According to his statement, he took 100 mg phenylhydrazin daily for 10 days of each month, for about two years. Also he had two courses, of 48 treatments each, of radiation over the long bones. He has epistaxis two or three times yearly which affords considerable relief. Bleeding has always given prompt relief. He has taken treatments wherever he happened to be, as he has moved about considerably.

Examination showed face, neck and extremities cyanotic. Moderate degree of pulmonary emphysema, cardiac hypertrophy and dilatation. Blood pressure 130 systolic and 80 diastolic. Liver enlarged and tender, spleen enlarged 6 cm below the costal border in the mid-clavicular line, not tender.

Laboratory: Hemoglobin 115, red blood cells 10,450,000, white blood cells 28,000, red blood cells show poikilocytosis and anisocytosis. Many large oval forms. Many rod-shaped cells. Urine showed heavy trace of albumin. 6–8 pus cells. 1–3 red blood cells per high dry field. 4–5 hyaline and granular casts per low power field. Basal metabolic rate 7 per cent plus. Oxygen capacity of blood 16.46 volume per cent. Blood sugar 102 mg per 100 cc.

There is a possibility of the erythrocytosis, in this patient, being connected with a pituitary tumor (presumably a basophilic adenoma) The following findings suggest this diagnosis

Roentgenogram findings suggestive of a pituitary tumor, a question of temporal narrowing of the fields of vision, exophthalmos, adiposity of face, neck and trunk, loss of libido, loss of hair, dusky congested skin, pigmentation of skin, polyphagia, polydipsia, polyuria

CASE III

Female, aet 68 Admitted to University of California Hospital, March 19, 1928
Past History Malaria aet 20 Aet 43 took five drops of Fowler's solution for one year for "eczema" Menopause aet 45, uneventful Appendectomy and cholecystectomy aet. 67 (1927), good recovery, much dental work, bleeding gums past four or five years

Complaints Weakness and swelling of lower extremities since 1923 (five years), burning of hands and feet, dizziness, failing vision, memory "bad" Thickness of tongue and difficult speech for two weeks before being seen March 19, 1928 Examination cyanosis of face, hands and feet, peripheral arteries sclerotic, radial arteries beaded, blood pressure 210 systolic and 100 diastolic, heart slightly enlarged to the left, heart sounds good quality, no murmurs heard, second aortic sound greater than second pulmonic, chest shows moderate pulmonary emphysema, abdomen liver enlarged, about six centimeters below the costal border in the right mid-clavicular line, spleen palpable, edge sharp and tender

Laboratory Blood hemoglobin 85, red blood cells 8,200,000, white blood cells 10,150, neutrophils 64, lymphocytes 35, monocytes 1, urine, specific gravity 1.015, acid, albumin moderate trace, sugar 0, sediment, few pus cells, occasional granular and hyaline cast Phenolsulphonephthalein 30 per cent first hour, 12 per cent second hour, total 42 per cent Ewald test meal, no free HCl, low total acid, no blood Electrocardiogram rate 88, regular rhythm, somatic tremor in Lead I; within normal limits Wassermann negative, blood chemistry, urea nitrogen 15.6 mg, non-protein-nitrogen 46.1 mg Stool negative for parasites, ova and blood

Patient had two courses of phenylhydrazin hydrochloride The first totaled four grams in 16 days Red cells dropped to 3,030,000 with 50 per cent hemoglobin, white blood cells 20,900 with 82 per cent neutrophils She began to complain of numbness and loss of motor power in the left arm and hand and a left facial weakness was noted Phenylhydrazin was discontinued The second course was given in another city after she left the hospital This course was accompanied by loss of memory, so the drug was discontinued

Diagnosis Polycythemia hypertonica (Geisbock's syndrome)

RESULTS

It will be noted that each table has a graphic chart accompanying it, bearing the same number The graphic chart shows the general results of the experiment, the table giving the details

Case No. 1, Chart No. 1 and Table No. 1 show the results of 10 venesections given to this patient These procedures were distributed over a continuous period from June 18, 1931 to November 4, 1931 There was an average, roughly, of two venesections per month for five months (169 days) The first three venesections were performed every fourth day, three full days elapsing between The highest reticulocyte rise of this first experimental period was 2.2 per cent, occurring four days after the third venesections

TABLE I

CASE 1

1931	Hgb per cent	R B C millions per cu mm	Retic per cent	W B C thou- sands per cu mm	P M N per cent	P M E per cent	P M B per cent	Lymph per cent	Monoc per cent
June	11	129	9 84	0 2	11 2	78		17	4
	18				Venesection—300 c c				
	19		9 22	0 3	6 0	57		38	5
	20		8 65	0 6	4 2	75	1	17	7
	22		8 43	0 9	6 1	69		27	3
	23				Venesection—200 c c			1	
	24		9 08	1 0	11 6	75		21	4
	25		9 17	0 9	7 4	67	3	26	4
	26		8 22	1 2	6 7	60	1	35	4
	26				Venesection—600 c c				
	27		7 99	1 8	8 6	65	1	25	9
	29	114	8 27	1 5	9 0	74	1	21	4
	30		7 28	2 2	9 4	74		22	3
July	1		7 69	0 8	8 9	60		37	3
	2		7 80	0 6	10 9	61	1	36	2
	3		7 60	0 2	9 4	70		26	4
	6	116	7 54	0 6	8 6	78	1	17	4
	7		7 24	1 6	10 0	74		21	5
	8		6 94	1 5	11 1	64	1	33	2
	8				Venesection—600 c c				
	9		7 54	1 6	12 2	74		24	2
	10		7 35	0 1	13 2	72	1	25	2
	11		7 31	0 8	15 5	64	1	31	4
	13	106	6 74	0 5	10 5	72	1	22	5
	14		6 90	0 8	13 4	50	2	43	5
	15		6 40	0 8	12 8				
	16		6 24	0 7	11 6	61		34	5
	17		8 05	0 7	11 0	61	1	32	6
	18	106	7 54	1 0	12 8	73		23	4
	20		6 84	0 3	11 0	66		30	4
	21		7 12	0 2	10 2	76	1	17	6
	22		7 45	0 4	9 9	69		26	5
	23		7 32	1 1	9 9	67		28	5
	23				Venesection—500 c c				
	24		6 71	0 6	11 2	57		36	7
	25		7 00	0 7	10 4	69	1	26	4
	27		6 92	0 8	9 9	74		21	5
	28		6 75	0 1	12 6	72	1	25	2
	29		6 91	0 8	9 0	67		27	6
	30		6 89	1 2	9 4	71	1	24	4
	31		6 44	0 8	9 0	63		34	3
Aug	1		6 67	0 8	11 1	65	1	27	7
	3		6 48	0 6	8 6	73	2	22	3
	4		6 20	0 8	8 7	67	2	26	5
	5		6 24	1 0	6 1	71	1	20	7
	6		6 80	0 9	6 8	71	1	24	4
	6				Venesection—600 c c				
	7		6 55	1 1	8 5	72		19	9
	8		6 08	0 9	10 8	70		22	8
	10		5 79	1 2	7 8	75		22	3
	11		5 91	1 4	10 4	73	1	15	10
	12		5 72	1 2	7 1	68		25	7
	13		5 67	0 5	8 0	64		31	5
	14		5 86	0 8	5 1	76		20	4
	15		6 12	0 8	7 0	74	1	23	2
	17		6 15	0 7	7 0	64		32	4
	18		6 18	0 7	6 4	70	2	21	6
	19		6 30	1 0	10 1	65	1	23	9
	20		6 28	0 3	7 3	64	1	23	12
	21		6 59	0 2		70		24	5

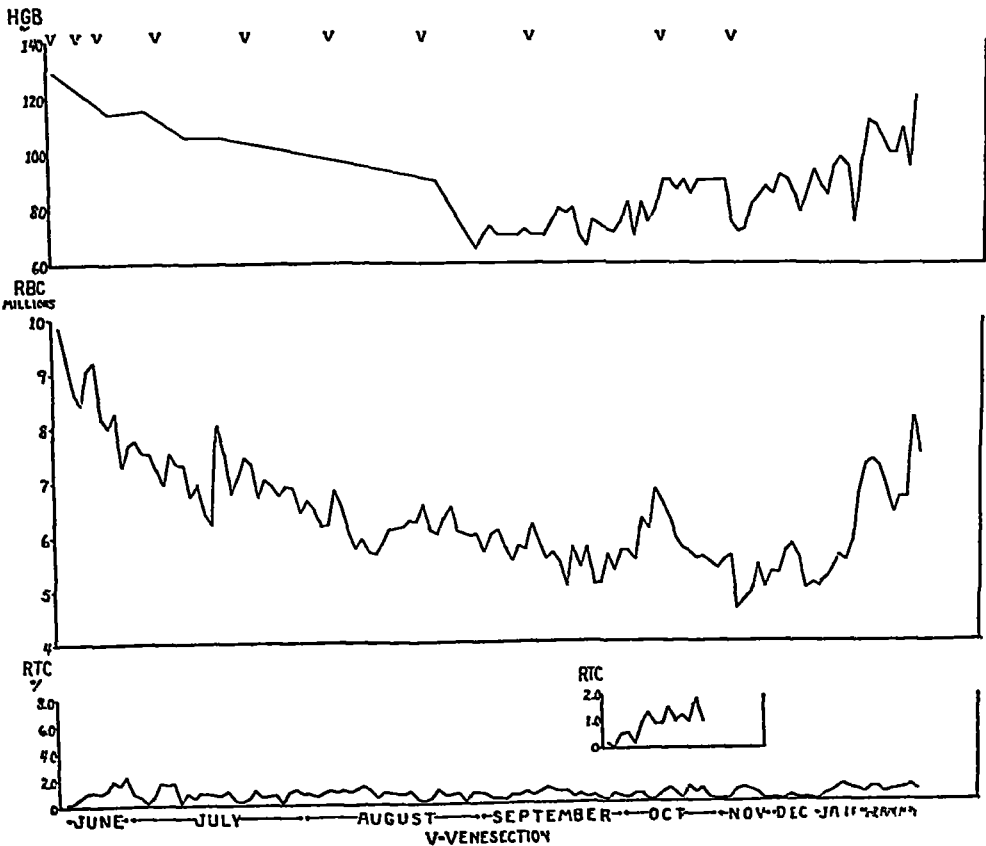
TABLE I (Continued)

1931	Hgb per cent	R B C millions per cu mm	Retic per cent	W B C. thou- sands per cu mm	P M N per cent	P M E per cent	P M B per cent	Lymph per cent	Monoc per cent
				Venesection—300 c c					
				96	59			28	13
	90	6 12	0 4	73	55			34	11
		6 03	1 1	78	67			29	4
		6 33	0 6	74	64			29	7
		6 54	0 7	117	73			21	6
		6 17	0 8	90	77	1		16	6
		6 08	0 1	88	75		1	16	8
	65	5 97	0 8	73	71			24	5
Sept	70	6 01	0 8	73	71			24	6
	70	5 75	0 7	60	70			38	9
	73	6 01	0 4	58	52		1	28	7
	70	6 11	0 4	54	65			37	8
		5 77	0 3	66	53	2		30	1
	70	5 55	0 6	91	69			25	5
	70	5 84	0 6	75	70			25	8
	72	5 72	0 8	43	66	1		28	5
	70	6 20	0 6	60	66	1			
				Venesection—400 c c					
			0 8		62	1		26	11
	70	5 58	1 2	58	58		1	35	6
	75	5 68	0 9	54	59			32	9
	80	5 48	0 8		67	1		27	5
	78	5 09	0 8	63	57			37	6
	80	5 79	0 4	92	62			31	7
	70	5 40	0 6	79	66			26	8
	66	5 78	0 4	48	60			32	8
	75	5 13	0 5	96	73	1		22	4
	73	5 17	0 3	76	69	1		24	6
		5 69	0 2		70			20	10
	72	5 30	0 6	53	73			22	5
	75	5 72	0 4	54	59			32	9
Oct	82	5 74	0 3	69	55			38	7
	70	5 56	0 6	103	70		1	25	4
	82	6 30	0 6	69	59		1	32	8
	75	6 11	0 2	65	62			30	8
	80	6 89	0 2	82	57	1		34	8
	90	6 67	0 6	104	54		1	32	12
				Venesection—600 c c					
	90	6 39	1 0	104	71			18	11
	87	5 93	0 6	89	52			38	10
	90	5 78	0 2	92	65			34	1
	85	5 72	1 2	91	67			23	9
	90	5 65	0 6	83	66		1	26	8
	90	5 67	0 1	113	62	1	1	31	3
		5 50	0 3	94	68	1	2	23	6
		5 39	0 2	86	73	1		22	4
Nov	90	5 53		88	63			29	8
	90	5 61	0 3	87	61	1		32	6
				Venesection—350 c c					
	75	4 64	0 8	84	53		3	36	8
	72	4 80	1 0	96	68		3	20	9
	73	4 90	0 8	83	58		2	30	10
	82	5 48	0 6	99	70	1		20	9
		5 04	0 2	80	59	1	1	33	6
	87	5 34	0 2	97	65		1	28	6
	85	5 30	0 2	82	68		2	26	4
Dec	92	5 73	0 1	104	54	1	1	33	11
	90	5 88	0 4	84	72		2	20	6
	85	5 66	0 2	81	49	1	1	36	13
	78	5 03	0 2	84	61	1		30	8
	85	5 17	0 1	86	73	2		16	9
	93	5 11	0 1	81	66	2		26	6

TABLE I (Continued)

1932		Hgb per cent	R B C millions per cu mm	Retic per cent	W B C thou- sands per cu mm	P M N per cent	P M E per cent	P M B per cent	Lymph per cent	Monoc per cent
Jan	5	88	5.23		10.6					
	8	85	5.43	0.7		74				8
	13	95	5.65	1.0	11.0	67	1	2	18	4
	16	98	5.56	1.2	8.0					
	21	85	5.88	0.8	9.7					
	27	75	6.62	0.8	6.9	68	1		24	7
Feb	13	97	6.81	0.6	7.8	72	1		26	1
Mar	5	112	7.34	1.0	8.5	58			30	12
	8	110	7.40	1.0	10.2	57	2		29	12
	11	105	7.31	0.6	10.6	68	1		26	5
	15	100	6.89	0.7	12.1	62	1	1	28	8
Apr	1	100	6.44							
	13	108	6.71	0.9	13.4	61			27	12
	20	95	6.70	1.2	10.3	64			29	7
May	16	120	8.16	0.8	9.4	72		2	20	6
	18		7.54	0.6	8.7	76	1	3	14	6

CASE 1—CHART 1



After each bleeding, the reticulocyte count rose to between 1 and 2 per cent, the rise occurring between 24 hours and four days (96 hours). It will be noted in inspecting Table No. 1 and Chart No. 1, that the reticulocyte count during the venesection treatment period varied within narrow limits. The average count for the period was .4 per cent.

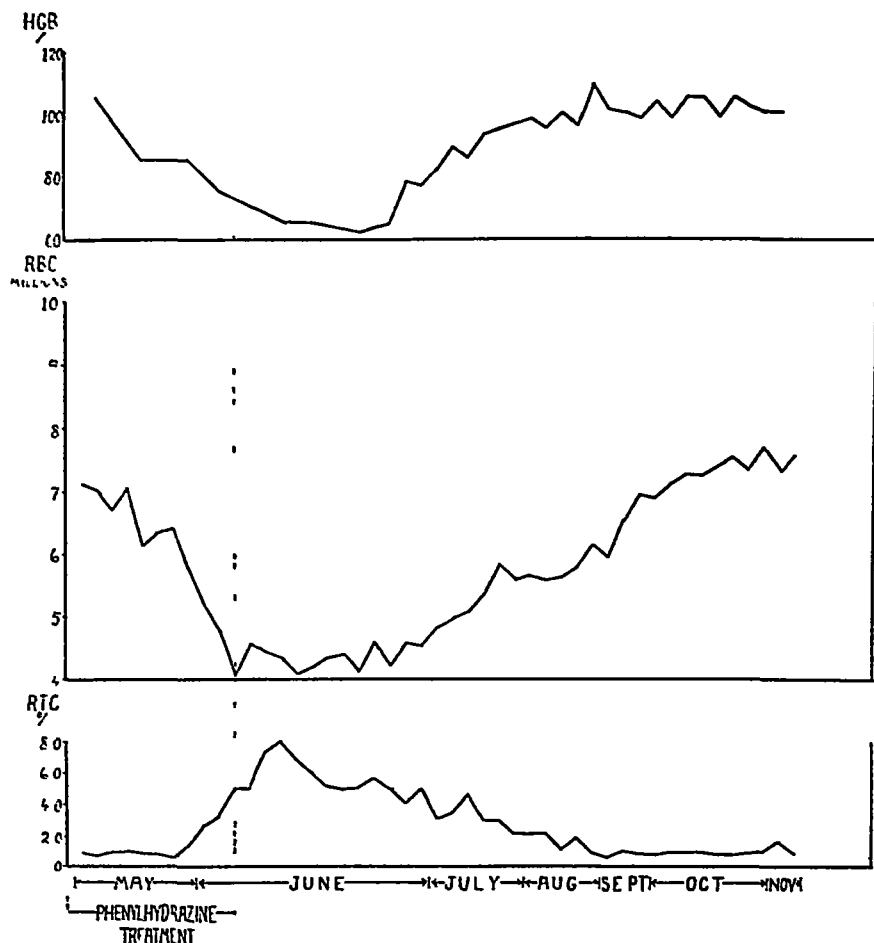
TABLE II

CASE 1

1932		Hgb per cent	R B C millions per cu mm	Retic per cent	W B C thou- sands per cu mm	P M N per cent	P M E per cent	P M B per cent	Lymph per cent	Monoc per cent
May	18				Started Phenylhydrazin					
	19		7 13	0 8	127	47			41	12
	20	105	7 06	0 7	13 6	69			25	6
	21		6 81	0 9	8 5	57			36	7
	23		7 09	1 0	8 0	61		4	31	4
	24	85	6 14	0 8	9 2	67			29	4
	25		6 31	0 8	12 1	67			24	9
	26		6 40	0 6	11 6	63			29	8
	31	85	5 84	1 3	13 4	61			26	13
June	1		5 18	2 6	12 8	74	1	1	19	5
	3	75	4 84	3 3	11 2	59			30	11
	5				Stopped Phenylhydrazin					
	6	63	4 02	5 0	11 5	67			27	6
	7		4 54	5 0	10 9	77			16	7
	8		4 43	7 4	10 2	70			28	2
	9	66	4 31	8 0	11 2	69	2	2	23	4
	10		4 07	6 8	9 6	68	2	2	21	7
	13	65	4 19	6 0	8 4	63	5	1	25	6
	15		4 31	5 2	9 6	71			26	3
	17		4 35	5 0	7 9	69	1		22	8
	20	62	4 10	5 1	9 6	71			21	8
	22		4 61	5 6						
	25	65	4 20	5 0						
	27	78	4 58	4 2	12 1	71		1	26	2
	29	77	4 55	5 0						
July	1	82	4 81	3 2	7 2	62	1	1	31	5
	6	89	4 97	3 5						
	9	86	5 08	4 3	7 1	73		1	22	4
	12	93	5 39	3 0	7 8	65			29	6
	15	95	5 84	3 0						
	19	97	5 60	2 1	7 7	71			21	8
Aug	2	98	5 68	2 1	6 1	67			24	9
	9	95	5 63	2 1						
	11	100	5 65	1 2	7 1	63	1		29	7
	15	96	5 78	1 8						
	26	109	6 15	0 9	6 9	65	1		30	4
Sept	2	101	5 93	0 6	8 3	58	2	1	31	8
	8	100	6 52	1 0	8 4	62			29	9
	17	98	6 95	0 8	5 7					
Oct	4	103	6 90	0 8	8 6					
	7	98	7 13	1 0	6 7	56	1		34	9
	10	105	7 27		5 6					
	13	105	7 26	0 9	7 0	65		1	27	7
	17	98	6 86	0 8	5 8	69		1	26	4
	21	105	7 57	0 8	7 8	68	2	3	22	5
	28	102	7 38	0 9	8 9	78			18	4
	31	100	7 71	1 0	10 2	70			18	12
Nov	5	100	7 32	1 6	10 2	70			26	4
	10		7 66	0 9	7 3					

Chart No 2 and Table No 2. The last venesection was November 4, 1931. No further treatment was given, the red cells and hemoglobin were allowed to rise until, by May 16, 1932, the hemoglobin had gone up to 120 per cent and the red cells to 8 16 million. On May 18, 1932 patient was started on acetyl phenylhydrazin (pyrodin) 0 1 gram daily for four days or

CASE 1—CHART 2



a total of 14 grams. There was a prompt fall in hemoglobin and red cells as is characteristic of this hemolytic agent. The reticulocytes began to rise about the sixth day after the drug was started and increased rapidly to 8 per cent, falling very slowly and gradually. Even as long as 65 days after phenylhydrazin was stopped, the reticulocyte per cent was 1.2 which corresponds to the highest reticulocyte per cent during the venesection treatment period.

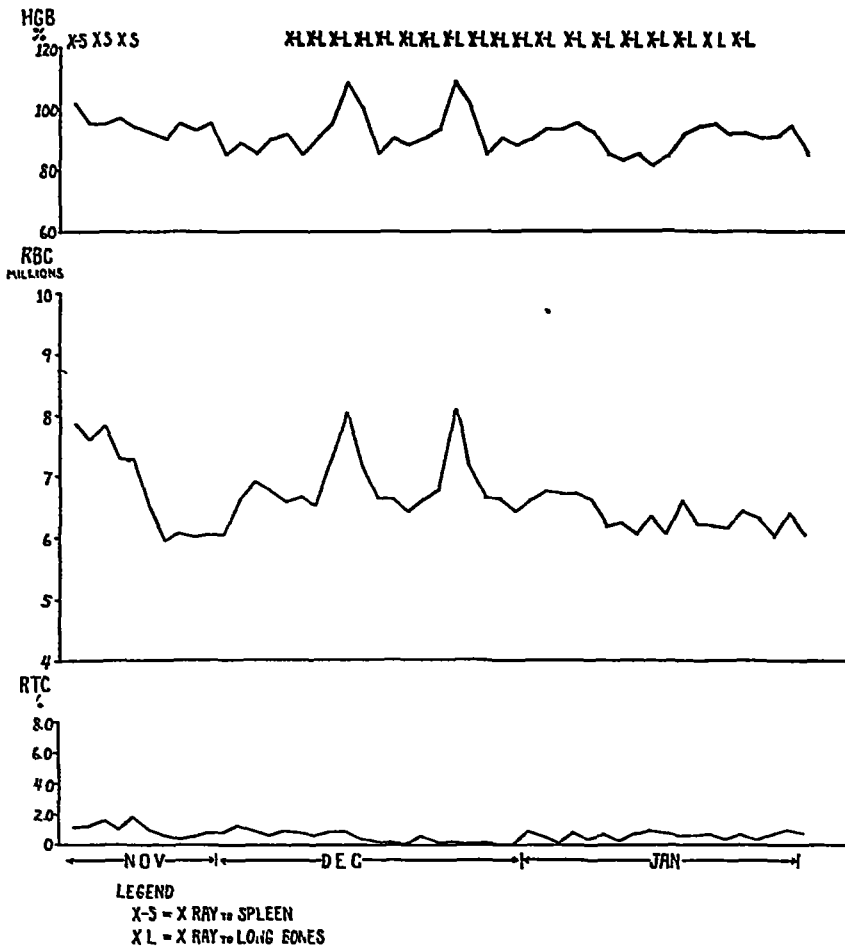
Chart No. 3 and Table No. 3 The red cells and hemoglobin following administration of phenylhydrazin were allowed to return to the level at which phenylhydrazin was begun, which occurred by November 17, 1932. On this date radiation was begun. Three exposures over the spleen with deep roentgen therapy were carried out at three day intervals. After two weeks, as there was only approximately one million reduction in her red cells, radiation was again given over the long bones, twelve treatments being administered. The reticulocytes were 1.2 per cent at the beginning of the treatment and none was noted on January 5, 1933, the date of the last treatment. The highest rise was 1.8 per cent, six days after radiation was begun, and it will be noted that the daily variation was within a very narrow range.

TABLE III

CASE 1

1932		Hgb per cent	R B C millions per cu mm	Retic per cent	W B C thous- ands per cu mm	P M N per cent	P M E per cent	P M B per cent	Lymph per cent	Monoc per cent
Nov	17	102	7 84	12	82	68			28	4
	17				X-ray to Spleen					
	18	95	7 63	13	52	68	1		19	12
	18				X-ray to Spleen					
	19	95	7 80	16	87	72			14	14
	21	97	7 30	10	64	76	1		15	8
	21				X-ray to Spleen					
	22	94	7 29	18	100	85	1	1	9	4
	23		6 49	10	84	80	2		9	9
	25	90	5 96	06	63	83			8	9
	26	95	6 20	04	73	85	1		5	9
	28	93	6 04	05	37	74	2	2	12	9
	30	95	6 10	08	55	86		1	10	13
Dec	1	85	6 08	08	78	68		2	16	12
	2	88	6 68	13	68	79	1		14	6
	3	85	6 90	09	95	81			11	8
	5	90	6 78	06	71	76		1	20	2
	6	92	6 66	09	66	75	1	1	16	6
	7	85	6 74	08	81	69	2	2	22	5
	7				X-ray to Long Bones					
	8	90	6 55	07	100	77		1	13	9
	9	95	7 26	09		68	1		18	12
	9				X-ray to Long Bones					
	10	108	8 05	09	130	74		3	18	5
	12	100	7 20	04	112	72	1		18	8
	12				X-ray to Long Bones					
	14	85	6 68	02	78	64	2		23	11
	14				X-ray to Long Bones					
	16	90	6 67	02	98	70	1	1	22	6
	16				X-ray to Long Bones					
	19	88	6 44	05	55	76		1	17	6
	19				X-ray to Long Bones					
	21	90	6 67	00	71	80	1	2	15	2
	21				X-ray to Long Bones					
	22	93	6 80	02	93	86	1	1	8	4
	23	93	6 77	01	75	72			21	7
	23				X-ray to Long Bones					
	27	95	6 77	01	65	69			19	12
	27				X-ray to Long Bones					
	28	92	6 65	01	62	75	2		13	10
	29	85	6 19		55	66	3	1	19	11
	29				X-ray to Long Bones					
	30	83	6 24	00	41	61			25	14
	31	85	6 07	00	44	78		1	15	6
	31				X-ray to Long Bones					
Jan	3	82	6 32	09	53	77	1		16	6
	3				X-ray to Long Bones					
	4	84	6 05	05	62	76	1		15	8
	5	92	6 63	00	52	70			21	9
	5				X-ray to Long Bones					
	6	94	6 24	08	66	71	1		17	11
	7	95	6 23	04	74	58			23	13
	9	92	6 20	07	41	75	1		16	7
	10	92	6 45	03	76	81			13	6
	12	93	6 31	07	46					
	13	91	6 02	10	64	72		1	15	12
	16	94	6 40	08	58	59			32	9

CASE 1—CHART 3



Case No 2, Chart No 4 and Table No 4 show the effects of venesection and of radiation in polycythemia secondary to chronic asthma and pulmonary emphysema. The venesections were not uniform in amount two of them being under 400 c c due to technical difficulties in bleeding the patient. It will be noted, however, that on December 29, 1932, after the radiation had reduced his cells to below five million, he was bled 850 c c. On the fifth day following, the reticulocyte per cent was 2.2, the highest rise of the experiment, including both venesection and radiation. The reticulocyte fluctuation during both venesections and radiation was within narrow limits. Exclusive of the last venesection, which came after the course of radiation, the reticulocyte per cent varied between 0.1 and 1.4 in both types of treatment.

Case No 3, Table No 5. This patient showed an acute polycythemia and was quite ill. As soon as his symptoms were relieved by venesection, he would leave the hospital, going to his home in another city, returning again when symptoms became distressing. He was not a cooperative patient for purposes of treatment, however his table shows very well the effects of large venesections combined with radiation over the long bones in an acutely ill polycythemia, possibly of the secondary type (see case record).

TABLE IV

CASE 2

1931	Hgb per cent	R B C millions per cu mm	Retic per cent	W B C thou- sands per cu mm	P M N per cent	P M E per cent	P M B per cent	Lymph per cent	Monoc per cent
Nov 3	110	6 90							
11	108	6 10							
1932									
Jan 21	117	6 40	0 3	63	62	2		24	12
25	112	6 23	0 2	44	51			34	15
26	108	5 95	0 2	69	62	1		33	4
26				Venesection—375 c c					
27	100	4 92	0 1	58					
Feb 1	90	4 32	0 1	56					
3	90	4 17	0 3	46	60			29	11
9	100	4 80	0 1	43	73	2		18	8
12	95	4 50	0 6	10 8	69			22	9
15	96	5 00	0 3						
19	107	5 18	0 2	5 4					
20				Venesection—500 c c					
23	104	4 92	0 2	6 1					
25	83	4 36	0 7						
29	95	5 21	0 6						
Mar 2	100	5 21	1 4	4 8	57	1	1	29	12
4	103	5 14	1 1						
7	96	5 02	1 2						
10	90		0 9	4 7					
15	100	5 42	1 1		69	2		24	5
17	100	5 02	0 8						
28	99	4 91	0 8						
30	100	5 47	1 0	3 7	52	2		34	12
Apr 4	110	5 44	0 4	5 4					
8		5 63							
19	110	5 83	0 6		54			36	10
26	104	4 90	0 2						
May 2	92	4 90	0 4	6 2					
9		5 22							
16	100	4 92	0 2						
June 3	102	5 18	0 4						
6		5 98	0 1						
7				Venesection—600 c c					
8	88	5 19	0 2						
13	102	5 48	0 2						
21	103	4 61	0 9						
24	102	5 28		5 2	56	4		32	8
Sept 20	105	5 73	0 2	4 1					
20				Venesection—350 c c					
21	103	4 75	0 2	6 1	45	2		41	12
23	100	5 05	0 4	5 6	56	2		32	10
24	110	5 04	0 4	3 9	55	1		32	12
27	102	5 40	1 0	4 3	62	2		25	11
Oct 3	105	5 34	0 6	6 8	56	2		35	6
6	103	5 18	0 8	5 0	45	2		42	11
6				X-ray to Spleen					
8	110	5 12	0 9	4 9	57	1		32	10
8				X-ray to Spleen					
11	105	5 37	0 6	4 7	55	2		28	15
11				X-ray to Spleen					
13	109	5 25	0 2	4 4	69	1		18	12
13				X-ray to Spleen					
15	104	5 24	0 6	4 5	72	1		17	10
15				X-ray to Spleen					
18	95	4 95	0 4	4 0	66	1		24	9
18				X-ray to Spleen					
21	93	5 20	0 2	4 5	66	1		25	8

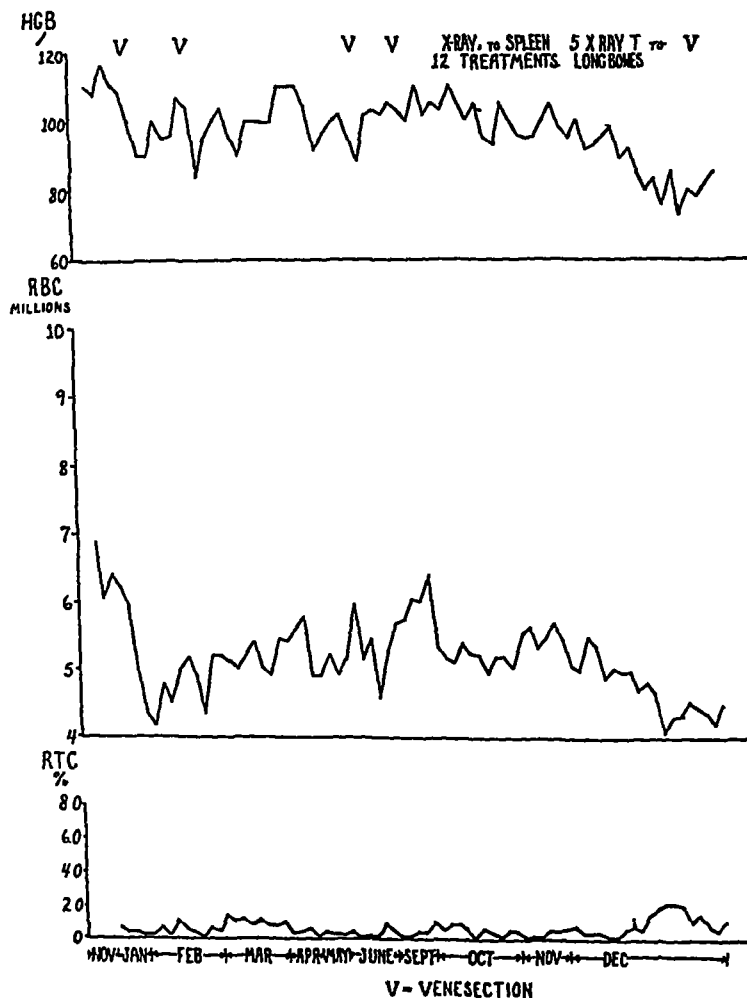
TABLE IV (Continued)

1932		Hgb per cent	R B C millions per cu mm	Retic per cent	W B C thous- ands per cu mm	P M N per cent	P M E per cent	P M B per cent	Lymph per cent	Monoc per cent
Oct	21				X-ray to Spleen					
	25	105	5.21	0.5	3.9	68	1		16	15
	25				X-ray to Spleen					
	28	101	5.06	0.4	4.9	68	2	1	15	14
	28				X-ray to Spleen					
Nov	10	96	5.52	0.2	3.6	70	2		14	4
	10				X-ray to Spleen					
	12	95	5.62	0.2	4.9	60	3		18	19
	15	95	5.31	0.2	5.4	64	2		26	8
	15				X-ray to Spleen					
	19	100	5.50	0.5	4.2	52	5		27	16
	19				X-ray to Spleen					
	25	104	5.67	0.5	4.0	70	1	1	13	13
	30	98	5.49		4.4	70	1		15	14
Dec	5	95	5.14	0.8	4.2	66	2		16	16
	5				X-ray to Long Bones					
	6				X-ray to Long Bones					
	7				X-ray to Long Bones					
	8				X-ray to Long Bones					
	8	100	5.01	0.4	4.0	60	3		19	17
	13	92	5.50	0.4	5.9	77	1		12	10
	15	93	5.34	0.4	6.4	72	2		12	14
	15				X-ray to Long Bones					
	19	95	4.88	0.2	5.9					
	20	98	5.03	0.2	5.9	74	1		15	10
	21	89	4.99	0.7		66	1		20	12
	24	92	5.00	0.8	4.9					
	27	85	4.74	0.6	8.2	67	4		19	10
	29				Venesection—850 c c					
	30	80	4.87	1.5	7.4	80	2		7	11
	31	83	4.71	1.9	5.4	71	2	1	15	11
1933										
Jan	3	76	4.10	2.2	5.9	78			15	7
	6	85	4.29	2.2	7.4	77	1	1	14	7
	8	73	4.32	2.0	5.8	71	4		16	9
	10	80	4.54	1.1	6.7	75	2		17	6
	11	78	4.44	1.5	5.6	65	2		27	6
	13	82	4.35	0.8	4.7	66	3		18	13
	14	85	4.21	0.6	6.0	61	4		20	15
	16		4.52	1.2	7.9	76			14	10

Here again the reticulocyte response was within a very narrow range. The per cent level is slightly higher throughout than in the other experiments where the same agents are employed. This reticulocyte level certainly suggests a slightly over-active marrow, yet venesection of as much as 900 c c did not appreciably increase the marrow activity.

Case No. 4, Table No. 6 This patient, an elderly woman with hypertension (polycythemia hypertonica), had three venesections during a 27 day period of experimental observation. The reticulocytes did not rise above 1.8 per cent and the fluctuation was within a very narrow range. The amount of blood withdrawn at each bleeding was comparatively small on account of the danger in this type of case, that withdrawing too much blood may produce thrombosis, either of veins or small arteries, especially a cerebral artery. Relief of symptoms should be the objective.

CASE 2—CHART 4



DISCUSSION

Case No 1 was an especially favorable patient for a study of this type. She has been under observation for seventeen years and the response of her disease to various forms of treatment is well known. For the past four years her symptoms have been mild, responding well to phenylhydrazin and to venesection. The response to radiation has not been so satisfactory. I have purposely tried to guard against untoward results during these experiments, as such results would probably result in loss of cooperation and opportunity for future studies. The withdrawal of an amount of blood exceeding 600 c c was considered to involve a risk of thrombosis.

Analysis of the effects of venesection as compared to acetyl phenylhydrazin, on the bone marrow shows a striking difference in the reticulocyte response, acetyl phenylhydrazin producing a rise as high as 8 per cent, while venesection showed no definite change in what might be regarded in an adult, as the normal range of daily reticulocyte variation.

It is evident from the reticulocyte response to phenylhydrazin that this

TABLE V
CASE 3

1932	Hgb per cent	R B C millions per cu mm	Retic per cent	W B C thou- sands per cu mm	P M N per cent	P M E per cent	P M B per cent	Lymph per cent	Monoc per cent
Aug 25	115	10 45		28 0					
26				Venesection—900 c c					
Sept 1	112	10 38		26 5	94	2		3	1
2				Venesection—300 c c					
2	110	9 95	1 6	14 1	93		2	4	1
5	90	8 01	1 3	14 8	90	2	1	3	5
6	100	8 50	1 5						
26	105	9 93	1 3	15 4	90	1		5	4
26				Venesection—400 c c					
27	108	10 39	1 6	24 2	85	5	3	6	1
27				X-ray to Spleen					
Oct 28				Venesection—900 c c					
29	90	7 89	1 1	28 7	91	1	2	4	2
31	88	7 71	0 9	26 2	91	2	1	1	5
Nov 2	84	7 66	1 3	27 0	94	1	2	2 5	0 5
3			1 6		91	3	2	2	2
4	88	8 09	1 2	25 0	95	1		2	2
4				X-ray to Spleen					
5	90	7 84	1 8	19 7	96		1	3	
5				X-ray to Spleen					
7	92	8 36	1 3	24 4	94			2	4
8	88	8 17	1 1	22 5	91	3	1	3	2
8				X-ray to Spleen					
9	83	7 60	1 0	19 4	94	2	1	2 5	0 5
9				X-ray to Spleen					
10		8 09	1 5	20 0	94		3	1	2
12	85	8 24	1 3	20 7	96	1		1	2
14	95	7 91	1 0	17 8	89	3	3	3	2
15	93	8 20	1 4		92	3	3		2
16	89	7 98	1 0	20 1	95	1		4	
Dec 5	95	8 59	1 4	15 6	94	3		2	1
5				X-ray to Long Bones					
6	90	8 33	0 7	17 5	91	1		3	5
6				X-ray to Long Bones					
7		9 10	0 7	16 1	88	5		5	2
8	94	9 02	1 1	22 3	93		1	4	2
8				Venesection—250 c c					
9	85	8 49	1 3	19 7	88	2	1	4	5
9				Venesection—600 c c					

patient's bone marrow was not in a depressed or unduly sluggish state, failing to respond to venesection. Radiation, even when applied over the long bones, did not alter the daily fluctuation in reticulocytes. There is need for more knowledge concerning response of reticulocytes to various types of marrow stimuli (hemolytic agents and marrow irritants), before we can interpret the striking difference in this patient, in the reticulocyte rise with venesection and with phenylhydrazin.

With the other three patients, the effects of venesection on the reticulocyte response were similar to Case No. 1. No noteworthy variation could be observed. In Case No. 2 the reticulocyte response to withdrawal of 850 c c. of blood indicates that the bone marrow was not depressed or greatly inhibited by his previous exposure to radiation.

TABLE VI
CASE 4

1931		Hgb per cent	R B C millions per cu mm	Retic per cent	W.B C thou- sands per cu mm	P M N per cent	P.M E per cent	P M B per cent	Lymph per cent	Monoc per cent
May	29		8 10							
June	2	92	7 14	1 6	13 8	82	1		8	7
	12				Venesection—500 c c					
	13			1 0						
	14			1 4						
	15			1 0						
	16		7 71	1 6	7 3	88	1		10	1
	17			0 8						
	18			0 8						
	19			0 4						
	20			1 2						
	21	84	7 27	1 4	11 5					
	21				Venesection—500 c c					
	23			0 8						
	24			1 7						
	25			1 8						
	26			1 0						
	27			1 4						
	28				Venesection—500 c c					
	29			0 6						
	30			0 8						
July	1	-	6 78	0 8	8 0	77	1		16	6
	2			0 4						
	3			0 0						
	5		6 68		10 3	90		1	6	3
	6			0 0						
	7			0 4						
	8			0 2						
	9	72	6 68	0 1	5 8	86			12	2

The striking effect of venesection in Case No 3 was the almost magic relief of symptoms (dyspnea, headache, weakness) Also the response of his reticulocytes to the blood loss shows that the bone marrow of an acute, intractable polycythemia is not unduly stimulated by this procedure It is obvious, however, that certain acute types of polycythemia cannot be satisfactorily treated by venesection alone

Case No 4 illustrates the inadvisability of the use of phenylhydrazin in elderly people with hypertension and polycythemia This patient had two courses of this hemolytic agent before her venesection studies were begun Each time the symptoms were made worse, especially weakness, paresis, mental confusion, dizziness and numbness of hands and feet Parkes¹⁰ suggests that the polycythemia is protective in these cases, as the work of the heart is lessened through there being more oxygen carriers in the circulation

CONCLUSIONS

1 The results of this study indicate that venesection, used as a means of reducing the red cells and hemoglobin in polycythemia, does not increase the reticulocyte per cent above normal limits

2 Radiation over spleen or over long bones in polycythemia, does not stimulate the bone marrow as indicated by the reticulocyte per cent. Due probably to its slow action in the reduction of the blood level, the average daily reticulocyte count was lower than following venesection.

3 In a patient with polycythemia vera, following the administration of 1.4 grams of acetyl phenylhydrazin, the reticulocyte count promptly rose to 8 per cent, gradually falling to normal over a period of 82 days.

4 The study suggests that venesection may be a useful adjunct to phenylhydrazin treatment by permitting much smaller doses of this drug to be efficient in maintaining an approximately normal blood level.

BIBLIOGRAPHY

- 1 ALLEN, E. V., and GIFFIN, H. Z. Experiments with phenylhydrazin. I. Studies in the blood. II. Studies on renal and hepatic function and erythropoiesis, *Ann Int Med*, 1928, 1, 655, 677.
- 2 GIFFIN, H. Z., and CONNER, H. M. The untoward effects of treatment by phenylhydrazine hydrochloride, *Jr Am Med Assoc*, 1929, xcii, 1505-1507.
- 3 BRATLEY, F. G., BURROUGHS, H. H., HAMILTON, D. M., and KERN, C. The effects of pyridin poisoning on the blood and hemopoietic system, with especial reference to the formation of Heinz-Ehrlich bodies in vivo and vitro, *Am Jr Med Sci*, 1931, clxxxii, 597-605.
- 4 LONG, P. H. Effect of phenylhydrazin derivatives in the treatment of polycythemia, *Jr Clin Invest*, 1926, ii, 315-328.
- 5 ALTNOW, H. O., and CAREY, J. B. A case of polycythemia vera treated with phenylhydrazin hydrochloride with special reference to changes in blood morphology, *Jr Lab and Clin Med*, 1927, xii, 597-606.
- 6 GEISBOCK, F. Die Bedeutung der Blutdruckmessung für die Praxis, *Deutsch Arch f klin Med*, 1905, lxxxiii, 363-409.
- 7 MINOT, G. R., MURPHY, W. P., and STETSON, R. P. The response of the reticulocytes to liver therapy, particularly in pernicious anemia, *Am Jr Med Sci*, 1928, clxxv, 581-599.
- 8 CUNNINGHAM, T. D. A method for the permanent staining of reticulated red cells, *Arch Int Med*, 1920, xxvi, 405-409.
- 9 HURWITZ, S. H., and FALCONER, E. H. The value of roentgen-rays and benzene in the treatment of polycythemia vera, *Jr Am Med Assoc*, 1918, lxx, 1143-1145.
- 10 PARKES, F. W. Polycythemia hypertonica, is polycythemia a somewhat favorable sign in high blood pressure cases?, *Brit Med Jr*, 1927, ii, 98.

POLYCYTHEMIA IN ASSOCIATION WITH PULMONARY DISORDERS*

By JAMES J WARING, M D , F A C P , and W B YEGGE, M D , F A C P ,
Denver, Colorado

IN 1919 Aldred Scott Warthin¹ published a clinical report and autopsy protocol entitled "A Case of Ayerza's Disease: Chronic Cyanosis, Dyspnea, and Erythremia, Associated with Syphilitic Arteriosclerosis of the Pulmonary Artery" Since this report, on the first case of this type to be recognized in the United States and the first to be recorded in English, increasing interest in the polycythemia secondary to chronic pulmonary disorders and to lesions of the pulmonary artery has been manifested in this country and in South America In this particular group the essential cause of polycythemia appears to be chronic anoxemia which stimulates the bone marrow to excessive erythropoiesis

The case which we present here is that of a high grade polycythemia, due, in the first place, to long standing bronchial asthma, chronic bronchitis and emphysema and, in the second place, to a break down of adaptation to long continued hard labor at an altitude of 10 000 feet

CASE HISTORY

(Asthma, chronic bronchitis, and emphysema, pneumonia, peribronchial pulmonary fibrosis, polycythemia, cyanosis, failure of acclimatization to high altitude, dyspnea, hemoptysis, hematuria, increasing anoxemia and polycythemia, hypertrophy of the right ventricle, dilatation of the pulmonary artery, subacute glomerulonephritis, dependent edema, cardiac insufficiency, terminal bronchopneumonia, death, necropsy)

J B, a Swedish lumber-jack, aged 45 years, was first seen May 3, 1926 At this time his chief complaints were: weakness, shortness of breath, tightness in the chest, headache, loss of appetite, loss of weight, and "pain in the stomach"

Past History For about 25 years this patient had been a lumber-jack Since 1920 he had worked almost uninterruptedly in Colorado at an altitude of 10,000 feet For ten years attacks of asthma had been frequent, but following a severe attack of pneumonia in September 1921, they became much worse In September 1925, while working at 10,000 feet altitude he noted for the first time cyanosis, increasing weakness, and shortness of breath In January 1926, he complained of exhaustion, epigastric distress, and headache aggravated by exertion He left camp and came to Denver (altitude 5280 ft) After a few weeks' rest he felt better but on exertion all his symptoms returned About April 1, 1926, attacks of asthma became more frequent, cough more troublesome and expectoration more profuse and occasionally bloody

Physical Examination May 3, 1926 The patient, a tall well-developed man, had slight cyanosis of the face and extremities The tonsils were small but pus could be expressed from both sides The teeth were in very bad condition The fingers were clubbed The lungs were hyper-resonant and markedly emphysematous Many

* Read before the American College of Physicians, Montreal, February 7, 1933

From the University of Colorado, School of Medicine, Denver

squeaking and groaning râles were heard throughout both lungs. The heart was slightly enlarged, the pulmonic second sound was accentuated. No murmurs were heard. The abdomen was tender over the liver, which was enlarged. The spleen was not palpable. The blood pressure was 100 millimeters of mercury systolic and 80 diastolic, pulse 90, respiratory rate 20, temperature 98.6 degrees, weight 180 pounds.

The urine contained albumin 1 plus, and in the sediment a few hyaline casts and many red blood cells. The gastric analysis showed free acidity 27 degrees and total acidity 44 degrees. The Wassermann reaction was negative. The red cell count was 6,100,000, hemoglobin (Dare) 80 per cent. The white blood count was 5600, the differential count: polymorphonuclears 79 per cent, lymphocytes 18 per cent, eosinophiles 3 per cent.

Course During the next few months the patient improved somewhat, then dropped from sight and was not seen again until December 1927. Contrary to advice he had been working for several months in a lumber camp at 10,000 feet elevation and all his former symptoms had returned with increased severity.

The physical examination now showed marked cyanosis of the face and extremities, a purplish red color of the mucous membrane of the mouth, slight edema of the feet, a faint systolic murmur over the heart and accentuation of the pulmonic second sound. The hemoglobin was 120 per cent. The red blood cell count was 7,210,000, the white blood cells 4600. The urine had a specific gravity of 1.030 and contained albumin 2 plus and a few hyaline and granular casts. The roentgenogram of the chest showed a slightly enlarged heart, an enlarged arch in the region of the pulmonary artery and marked bilateral pulmonary fibrosis. The roentgenograms of the sinuses showed clouding of the antra on both sides, especially on the left.

The electrocardiogram (figure 1) showed the usual signs of marked right ven-

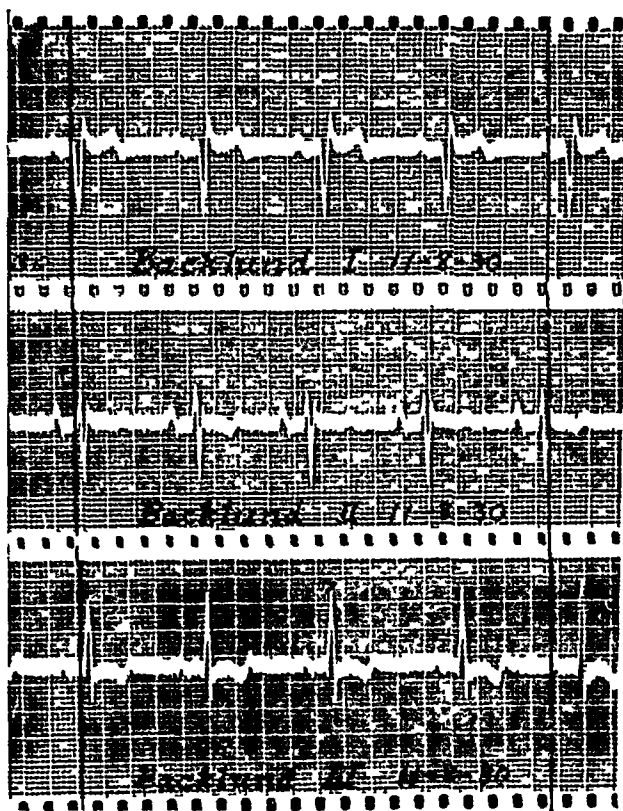


FIG 1 Electrocardiograms showing marked right ventricular preponderance and inversion of T-waves in Leads II and III

tricular preponderance and changes in the T-wave and ST interval in Leads II and III which during life were interpreted as indicating coronary disease. The basal metabolic rate was 60 plus. The blood sugar was 82 milligrams, urea 20 milligrams, and non-protein-nitrogen 36 milligrams per 100 cubic centimeters of blood. The Wassermann reaction was repeatedly negative. The sputum was always negative for tubercle bacilli. The patient remained in the hospital until February 1, 1928. During this time his tonsils were removed. The operation was followed by much bleeding and the red cell count dropped to 5,200,000 and hemoglobin to 100 per cent. Nine days later the count had risen to 7,270,000 and the hemoglobin to 118 per cent.

In June 1928, after working for two months in the mountains he returned in bad shape. The urine contained 4 plus albumin and many hyaline and granular casts. The red cell count was 7,290,000, hemoglobin 120 per cent and the white cell count 5600. A few weeks' treatment in bed brought some improvement.

From this time on the history of this patient up to the last few months of his life, when he was too incapacitated to work, was a repetition of the cycle of work in the mountains, relapse, hospital treatment in Denver, improvement, return to work in the mountains, relapse again. The spleen was never palpable, but the liver edge usually could be felt. The red cell count reached a maximum of 8,370,000, and cyanosis and dyspnea increased slowly but steadily. Somnolence was a conspicuous symptom.

During the last four years of his life hemoptysis always occurred shortly after his return to work in the mountains. On several occasions he had small hemorrhages from the lungs. Dyspnea and weakness increased until work was impossible and return to a lower altitude imperative. It is also significant that rest in bed in Denver without any medication whatsoever usually brought about a decided improvement in symptoms, a reduction in the size of the heart, a decrease in the red cell count and complete disappearance of albumin and casts from the urine. Figure 2 shows the change in the size of the heart brought about by six weeks' work in a lumber camp. M R increased from 32 to 46 centimeters, M L from 12 to 13.7 centimeters, L D from 15 to 18.2 centimeters. During the same interval the red cell count increased 40 per cent.

On June 24, 1929, he entered the Mayo Clinic*. We are indebted to Dr. George E. Brown for the privilege of using here the following notes of his examination at the Clinic. The figures for the blood volume at two examinations were 152 and 168 cubic centimeters per kilogram. The red cell count was 5,970,000, hematocrit 74 per cent (normal 45 per cent), blood viscosity 6.3, hemoglobin on admission 25 grams and on leaving 19.2 grams per 100 cubic centimeters of blood. The electrocardiogram indicated right ventricular preponderance and a slightly delayed conduction time. Roentgenographic examination of the chest showed marked fibrosis of both lungs with bronchiectasis of the left lower lobe. He was given two courses of phenylhydrazine with a rest of two weeks between courses and was discharged much improved with a red cell count of 4,800,000 and hemoglobin 80 per cent.

In March 1930, the red cell count was 8,370,000 and red cell volume by the hematocrit 82 per cent.

Dr. R. W. Danielson examined the eyes and reported, "Marked bluish redness of the conjunctiva of each eye, especially the left (with the biomicroscope the coloration is seen to be due to a myriad of dilated blood vessels rather than to hemorrhage), some pigment on the anterior capsule of the left lens from an iritis six months previously, many fine, white, round, scintillating floaters in the vitreous of the right eye, extreme tortuosity of the arteries and veins of the fundi, with increased blueness and size of the veins, increased redness of the discs which were otherwise normal except

* Nelson W. Barker of the Mayo Clinic reported this case as one of polycythemia vera in which the pulmonary condition was either an unrelated complication or secondary to pulmonary stress. (Barker, N. W. Polycythemia vera and chronic pulmonary disease. *Arch. Int. Med.*, 1931, *xliii*, 94-103.)

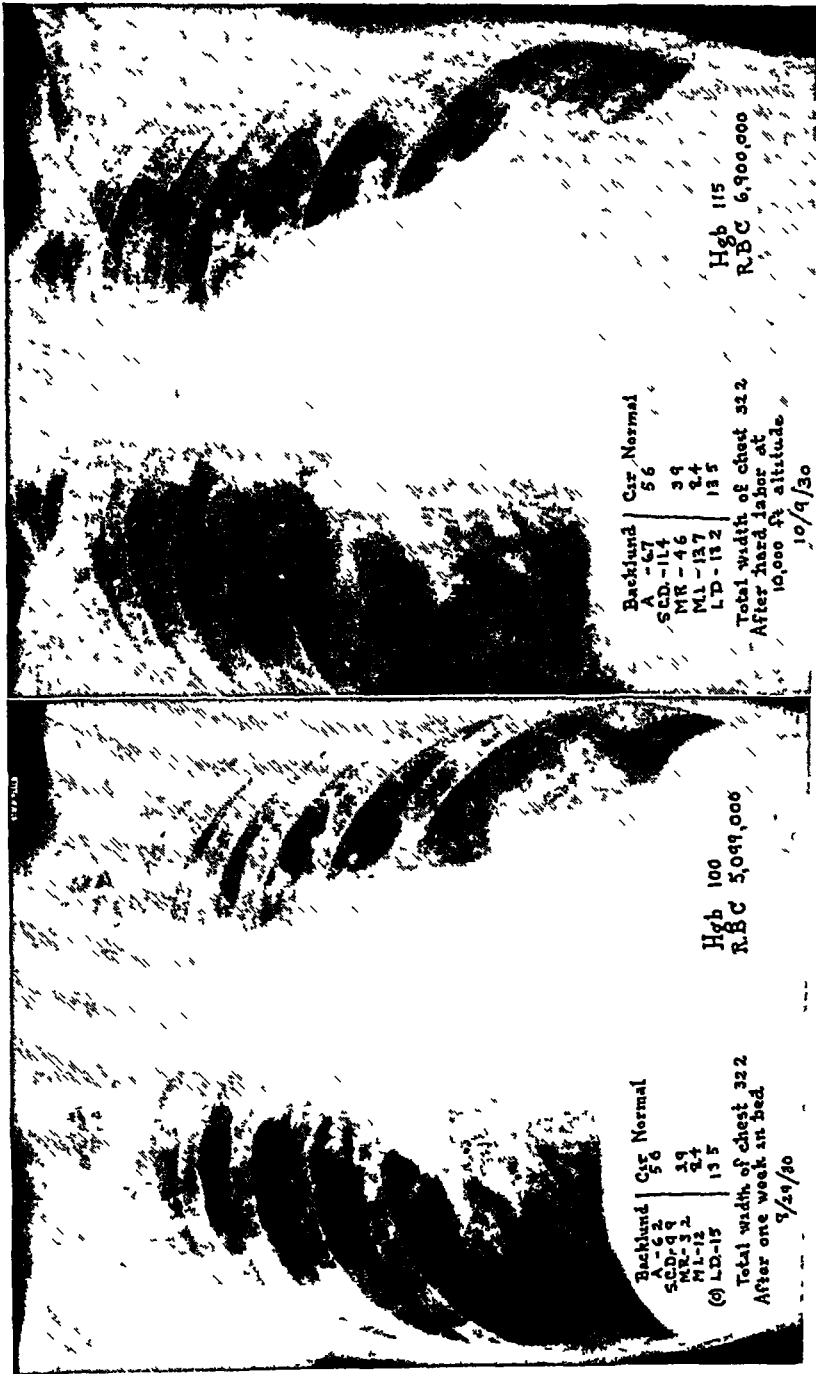


FIG 2 Teleroentgenograms showing effect upon the heart of six weeks' labor at altitude of 10,000 feet All dimensions are increased

for slight blurring of the nasal side of the left disc no exudates or hemorrhages of the retina: visual acuity (with small correction) O.D. 5/5, O.S. 5/6"

In spite of rest, change of residence to sea level digitalis, repeated venesections, courses of phenylhydrazine and finally radiotherapy of the long bones, he went downhill more or less steadily and finally entered the Denver General Hospital in very bad condition. Both lower extremities were swollen to the hips the hands, forearms and genitalia were edematous. The red cell count was down to 4,680,000, hemoglobin 90 per cent. The percentages in the differential count were polymorphonuclears 48, lymphocytes 43, mononuclears 3 eosinophiles 6. Pulmonary edema increased and death came April 3 1931, with all the signs of failure of the right side of the heart and a terminal pneumonia.

DIFFERENTIAL DIAGNOSIS

In the diagnosis it was necessary to consider three different conditions: (1) polycythemia vera with a pulmonary complication, (2) "Ayerza's disease," the syndrome of the "black cardiac" (cardiacos negros) or obstruction in the lesser circulation, (3) polycythemia of high altitude.

Polycythemic Vera Since this man had a greatly increased blood volume, it is more than possible that he had a primary erythremia. Against this diagnosis it may be stated that: (1) He had two well recognized causes for anoxemia a chronic pulmonary disorder and dys-acclimatization; (2) he was not erythrouc but intensely cyanotic; (3) a decrease in the blood count and a coincident reduction in the size of his heart usually followed rest in bed at a lower altitude, increase in the blood count and dilatation of the heart usually followed work at 10,000 feet; (4) he did not have an enlarged spleen; (5) instead of showing the leukocytosis characteristic of polycythemia vera his white blood count was always below normal; (6) the cells in the stained blood smear showed none of the qualitative changes that usually accompany polycythemia vera; (7) marked dyspnea is not part of the picture of polycythemia vera; (8) hypertrophy of the right ventricle is not a characteristic finding in polycythemia vera; (9) cyanosis, polycythemia, dyspnea, headache, nausea, loss of appetite and loss of weight, epigastric distress and hemoptysis together present a perfect picture of chronic mountain sickness; (10) somnolence although it occurs occasionally, has never been noted as a common symptom in polycythemia vera but it is frequently found both in "Ayerza's disease" and in the erythremia of high altitude as described by Monge.² Arullaga³ says of the "black cardiac": "They live to sleep fall asleep while eating and die in their sleep." It is possible that some of the reported cases in which somnolence has been recorded were really instances of "Ayerza's disease." Monge says of the victims of chronic mountain sickness "They have an insuperable tendency to sleep."

According to Harrop⁴ the respiratory symptoms in polycythemia vera are rather conspicuous. He notes a reduction in vital capacity and an increased respiratory minute volume, and states that "Dyspnea on much exertion is the rule." It will be recalled that Osler⁵ in his original article in 1903 on "Chronic Cyanosis with Polycythemia etc." wrote "There is no respiratory distress with the cyanosis." Also Warthin⁶ in 1919 in the fol-

lowing words emphasized the importance of dyspnea as a symptom characteristic of secondary polycythemia and not of primary erythremia "Does a primary erythremia exist? The writer believes not, certainly not in cases showing chronic cyanosis and dyspnea Why should a case of pure or absolute polyglobulism have either cyanosis or dyspnea? On the other hand, there is every reason why a case of chronic cyanosis and dyspnea should develop a chronic erythremia It is most probable that all erythremias associated with cyanosis and dyspnea (with a theoretical exception of a neoplastic overformation of red cells, yet to be definitely shown to exist) are *compensatory* in nature (secondary to pulmonary sclerosis, emphysema, congenital heart lesions, chronic pulmonary diseases leading to insufficient oxygenation, increased resistance of the red cells with lessened oxygen carrying capacity, etc)" Towards the end of the same article Warthin says "The erythremia in Ayerza's disease is beyond question a secondary compensatory process, an increased functional activity of the bone marrow to meet the deficiency in oxygen supply due to the obstructed pulmonary circulation It is most probable that this is the case in all forms of Vaquez' disease, certainly in all of those in which there is cyanosis and dyspnea Neither one of these symptoms belongs to a primary erythremia, and when they are present it is certain that the erythremia is secondary "

In regard to the other listed objections to a diagnosis of polycythemia vera, it must be admitted that none of them individually is conclusive The color of the skin and the qualitative changes in the blood in primary erythremia are variable, the spleen is not always enlarged, a reduction in the albumin of the urine after rest is not infrequent, orthostatic albuminuria has been described and, finally, Osler in 1903 noted the striking resemblance of the symptoms of this disease to mountain sickness

The very high values (167 cubic centimeters per kilogram of body weight) for the blood volume in polycythemia vera as determined by Rowntree and Brown ⁶ and Brown and Giffin ⁷ and the low values (93 cubic centimeters per kilogram) found by Lemon ⁸ in cases of pulmonary emphysema and bronchitis with cyanosis indicate the great diagnostic importance of a high blood volume in separating primary erythremia from a secondary polycythemia The high volume in our case is strong evidence in favor of polycythemia vera Rowntree and Brown say. "We believe that increases in the blood volume to 115 or 120 cubic centimeters for each kilogram of body weight, rarely or never occur as responses of the blood to lowered oxygen tension Whenever values in excess of these are found, we are of the opinion that they are more likely to represent the condition of true or primary polycythemia, perhaps in an early stage" This opinion is based upon the examination of a great variety of blood conditions but does not include a case of chronic failure of acclimatization similar to the *érythémie de l'altitude* described by Carlos Monge,² and includes only one case of "Ayerza's disease", this case had a blood volume of 114 cubic centimeters per kilogram of body weight although the number of erythrocytes was only

4,520,000 for each cubic millimeter of blood In *érythrémie de l'altitude*, a malady common to the Andes where a population of six million people live at an altitude over 10,000 feet, Monge finds the blood volume very high Unfortunately no estimations were made on these cases either by the dye or the carbon monoxide method but reliance has been placed on the hematocrit, which in an unstated number of the "indigenous acclimated" at 13,000 feet averaged 63.3 per cent This may be compared with an average value of 62 per cent in 14 cases of polycythemia vera reported by Brown and Giffin Monge reports one patient with very severe symptoms of dys-acclimatization who had a cell volume of 93.8 per cent Smith, Belt, Arnold and Carrier⁹ found a slight increase of the blood volume in healthy subjects during the process of adaptation to a brief sojourn at 8000 feet and in the Pikes Peak expedition of 1913, Douglas, Haldane, Henderson and Schneider¹⁰ noted a moderate increase in blood volume A true plethora has been found experimentally by Jaquet and Suter¹¹ in rabbits kept at Davos, altitude 5000 feet, and this observation has been confirmed by Guillemard and Moog¹² on rabbits at the summit of Mont Blanc These are, however, normal responses to high altitude and it is the abnormal responses in which we are particularly interested

In 1902 Lorrain Smith and McKisack¹³ reported a case of a boy of 12 years in whom cyanosis and plethora occurred in association with tuberculous pericarditis By the carbon monoxide method they found a blood volume of 115 cubic centimeters per kilogram body weight, which must be compared with a normal of 46 cubic centimeters per kilogram for this test By the dye method, in which the normal is 87.7 cubic centimeters per kilogram, the value for the blood volume for this boy would certainly have been much above 125 cubic centimeters F Parkes Weber and Dorner¹⁴ report a case of congenital pulmonary stenosis in which C Gordon Douglas found by the carbon monoxide method a blood volume value of 131 cubic centimeters per kilogram Haldane¹⁵ says he found a similar increase in another case In 1931 Binger¹⁶ reported a case with a blood volume by the dye method of 123 cubic centimeters per kilogram body weight and cyanosis and polycythemia from cardiac and respiratory failure that offered much the same difficulties in diagnosis as does the one in this paper

Apparently the pathologists are not convinced that polycythemia vera is the only condition in which a large increase in blood volume is found The latest edition of MacCallum's "Textbook of Pathology" has this passage (page 457): "Indeed, one receives the impression from observing the amount of blood in the vessels at autopsy in cases of long-standing chronic passive congestion from cardiac lesions, that there is a great increase in its quantity" Blood volume estimations have not been made on many cases of congenital heart disease of the cyanotic group Unfortunately they have also been omitted in a number of cases of manifest secondary polycythemia of very high grade where a high blood volume, if it ever occurs under such conditions might have been found It is hoped that our Spanish-American

neighbors to the south will apply the dye test to the "black cardiac" as well as to cases of *érythémie de l'altitude*

Although the number of determinations of blood volume in secondary polycythemia is insufficient to permit us to say how often the blood volume is increased and how high a figure may be reached, nevertheless the evidence favors the view that in this group of cases the blood volume is occasionally much increased

"*Ayerza's Disease*" Our patient presented a picture closely resembling that of so-called "Ayerza's disease" or obstructive pulmonary arteriosclerosis, the essential features of which are cyanosis, dyspnea, polycythemia and right ventricular hypertrophy. To the victims of this malady, more common in South America than in the United States, Abel Ayerza,³ Professor of Clinical Medicine at the National University of Buenos Aires, in 1901 applied the term "cardiacos negros" or "black cardiacs" to emphasize their persistent intense cyanosis and the associated cardiac disorder. Table 1

TABLE I
Summary of Essential Features

Ayerza's disease	Case J B
1 A long period of symptoms referable only to the lungs	1 Asthma 10 years, pneumonia and chronic bronchitis 5 years before onset of cyanosis
2 A temporary erythrosis, later cyanosis months or years before signs of marked decompensation	2 Marked cyanosis at least four years before death
3 Dyspnea	3 Dyspnea was an early symptom associated with asthma, chronic bronchitis and emphysema and was much aggravated after pneumonia in 1921
4 Polycythemia	4 Polycythemia 6 to 8.5 millions
5 Somnolence	5 Somnolence a very conspicuous symptom
6 Roentgenographic signs of right ventricular hypertrophy and dilatation of the pulmonary artery	6 Roentgenogram of heart and lungs showed right ventricular hypertrophy, dilatation of the pulmonary artery and chronic pulmonary fibrosis and emphysema
7 Electrocardiographic signs of right ventricular preponderance	7 The electrocardiogram confirmed the diagnosis of right ventricular hypertrophy

illustrates the perfect correspondence between the syndrome of Ayerza and the essential features of our case. Of the nine cardinal symptoms of "Ayerza's disease" mentioned by Arrillaga,³ viz., cyanosis, polycythemia, clubbing of the fingers, dyspnea, hemoptysis, headache, somnolence, hypercyanotic angina and angina pectoris, all in greater or less degree, were present in our case.

Polycythemia of High Altitude The anoxemia due to the lowered oxygen tension of high altitude and the excessive demands of severe exertion in a rarefied atmosphere certainly played an important part in this case. Carlos Monge,² Professor of Clinical Medicine at Lima, Peru, has been a prolific writer on what he calls *érythémie de l'altitude* and *maladie des Andes*. According to Monge, to become acclimatized it is necessary to pass through a preliminary stage of adaptation during which one manifests symptoms of

acute or subacute erythremia. If at the outset the adaptative mechanism fails quickly the result is acute mountain sickness, if the failure is prolonged over months, perhaps years, the result is chronic mountain sickness. Finally, if after acclimatization the mechanism of adaptation may break down, then one suffers from *dys-acclimatization*. In all of these instances erythremia may be found in greater or less severity. Monge states emphatically that if the biologic mechanism of adaptation fails one sees develop the symptomatology of the *maladie de Vaquez* and that this form of chronic erythremia can appear in subjects born at high altitude, in residents acclimated since infancy and even in the indigenous of pure race. The early stages are characterized chiefly by an erythremia which lasts two to ten years and by acute crises and spontaneous remissions in symptoms which are essentially those of mountain sickness, namely, cyanosis, polycythemia, dyspnea, vomiting, nose bleeds, hemoptyses, enlargement of the spleen, weakness and somnolence. On return to sea level all of these symptoms disappear. Death results from hemorrhage, pulmonary thrombosis, bronchopneumonia, cardiac insufficiency, or renal failure.

Finally Monge notes the close resemblance of *érythrémie de l'altitude* to "Ayerza's disease" from which it differs chiefly in the absence of sclerosis of the pulmonary arteries and one might add by its complete relief on return to sea level. Monge says among all these different erythremias there is one common bond, a functional disturbance of the pulmonary physiological element, the alveolus. "One should study functional respiratory syndromes as one studies those of Bright's disease." "If the functional troubles follow a chronic bronchial pneumonia or a pulmonary arteritis we have the syndrome of cyanosis and erythremia known as Ayerza's disease." The long drawn out picture of chronic mountain sickness is "absolutely analogous to *maladie de Vaquez*."

Return to sea level did not give complete relief to our patient, in the first place because he did not stay permanently, and, in the second place, because the pulmonary condition, asthma, chronic bronchitis, emphysema, and slowly increasing pulmonary fibrosis, had become a potent cause of anoxemia.

Monge does not explain why the mechanism of adaptation fails, but L. Ayerza, Solari and Berconsky¹⁷ believe it to be due to a diminution in the pulmonary minute ventilation. In chronic mountain sickness there is a compensated gaseous alkalosis in contrast to "Ayerza's disease" in which there is a chronic compensated gaseous acidosis. L. Ayerza, Solari and Berconsky found the composition of the alveolar air in a "black cardiac" to be O₂ 7.24 per cent, tension 51.47 mm Hg, CO₂ 9.49 per cent, tension 67.47 mm Hg (corresponding normal figures at sea level are O₂ 14 per cent, tension 103 mm, CO₂ 5 per cent, tension 40 mm). In other words the oxygen tension of the alveolar air in this patient was about that of a normal acclimated person on top of Pikes Peak (14,110 ft) and the percentage oxygen in the alveolar air was dangerously close to the critical level at which cardiac glycogen would be depleted and cardiac failure ensue.

(Meakins¹⁸) A great diminution was noted in the oxygen saturation of the arterial blood which was 81.9 per cent instead of a normal of 95 per cent. The vital capacity 1540 cubic centimeters and tidal air 170 cubic centimeters were both much reduced. The minute volume ventilation of the lungs was 4.6 liters as compared with a "normal of 7 liters." The respiratory volume per kilogram of body weight was 69 cubic centimeters (normal 110 cubic centimeters) and the respiratory volume per square meter body surface was 2624 cubic centimeters (normal 4097 cubic centimeters). When this patient was tested with atmospheric air containing 3.23 per cent CO₂, his respiratory minute volume went up from 5235 to 9440 cubic centimeters and his tidal air from 186 cubic centimeters to 248 cubic centimeters. This is a distinguishing feature from ordinary emphysematous cases in which Meakins found a great tolerance for high percentages of CO₂.

The basal metabolic rate (plus 60) in our patient was very high. At the time the test was made the red cell count was 5,200,000 and the pulse rate only 68, after two weeks of digitalis. Hurtado and Monge² have studied the metabolic rate in visitors and residents at high altitudes and find that it varies markedly with the state of acclimatization of the individual. In the indigenous acclimated the rate is normal. In acute mountain sickness it is decidedly below normal (average minus 26 per cent in four cases of Monge), in severe *érythémie de l'altitude* it is high (average plus 29 per cent in six cases of Hurtado with variations from plus 16 per cent to plus 67 per cent). In chronic cases of mountain sickness the basal metabolic rate increases progressively to reach a high figure in the most severe cases. In the acute forms of mountain sickness the pulse rate is very fast, in the chronic forms it is also above normal.

In the severe erythremias of high altitudes evidently a vicious circle is established. The high basal metabolic rate creates a demand for oxygen which cannot be satisfied except by return to sea level. Our man did not have manifest thyroid disease, but it is pertinent to recall that patients with hyperthyroidism and a high metabolic rate suffer more readily and more severely from anoxemia (Boothby¹⁹). It is equally well known that anoxemia causes the normal mammalian heart to dilate (Barcroft,²⁰ Katz and Long,²¹ Meakins¹⁸). In our patient the dilatation of the heart must have been due to the combined effects of severe exertion, low oxygen pressure and high basal metabolic rate. Since normal coronaries were found at the postmortem examination, it is possible that the abnormalities in the T-wave and ST interval in the electrocardiogram were due to anoxemia. The marked clubbing of the fingers was one more sign of inefficiency of both respiratory and circulatory systems.

A high basal metabolic rate is frequently found in polycythemia vera. Minot and Buckman²² thought the cases with the highest rate showed the greatest bone marrow activity. Brown and Giffin in tests on seven cases found the rate close to normal in four and elevated, plus 22 to plus 44, in three. They thought the higher rates were somewhat related to the higher

levels of total blood volume In general a close relationship between the basal metabolic rate and the red cell count is not usually found

Our conception of the evolution of the disability in this man may be summarized as follows Long-standing bronchial asthma and emphysema produced a low grade anoxemia which was greatly aggravated by severe exertion at a high altitude An excessive response by the bone marrow to the stimulus of chronic anoxemia induced a high grade polycythemia The burden of pumping an increased volume of a more viscous blood through a reduced capillary bed added to the strain upon the heart A metabolic rate rising with increased marrow activity magnified the bad effect upon the heart of an increasing anoxemia Periodic failure of compensation coincident with the visits to high altitude furnished a forceful stimulus to erythropoiesis by a more or less rhythmic aggravation of anoxemia

CLINICAL DIAGNOSIS

Polycythemia secondary to chronic pulmonary disease and to failure of acclimatization, pulmonary arteriosclerosis, chronic bronchitis, asthma and emphysema, periodic insufficiency of the right side of the heart, hypertrophy of the right ventricle, dilatation of the pulmonary artery, chronic glomerulonephritis, chronic sinusitis, terminal pneumonia

PATHOLOGICAL REPORT

The necropsy was performed by Dr W S Dennis, pathologist at the Denver General Hospital, the microscopic sections were examined by Dr W C Johnson, Professor of Pathology, University of Colorado School of Medicine From their reports are extracted the following notes

All the venous channels in the splanchnic region, especially the hepatic vein and portal vein, and the pulmonary artery and its branches throughout the lungs are much dilated The heart is much enlarged, its weight 675 grams (normal 300 grams) The left ventricular wall has a maximum thickness of 20 millimeters (normal 12.5 millimeters), the right ventricular wall a maximum thickness of 14 millimeters (normal 3 to 4 millimeters) The valves and coronaries are normal The circumference of the pulmonary artery just above the valve is 10 centimeters (normal 8 centimeters) On the intimal surface of the pulmonary artery and its primary branches are numerous subintimal yellowish patches The aorta, except for a few yellowish plaques, closely approximates the normal The liver weighs 1800 grams and everywhere shows marked dilatation of the venous channels The spleen is normal in size The kidneys are not remarkable in appearance The bone marrow of the femur and ribs is of a deep brick red color The lungs show moderate thickening of the pleura, consolidations in the left lower lobe and lower part of the left upper and right lower lobes, moderate emphysema and some bronchial dilatations

Microscopic examination shows a slight infiltration of the epicardium of the wall of the left ventricle with lymphocytes and large mononuclear cells The muscle fibers appear normal but scattered between them is a slight infiltration with lymphocytes and large mononuclear cells These cells are more abundant in the connective tissue septa around the blood vessels but there is no Aschoff body formation

The muscle fibers of the wall of the right ventricle are moderately hypertrophied (figure 3) The wall of the right auricle shows slight fibrous thickening of the endocardium and the muscle fibers show moderate hypertrophy In a few places in the endocardium and between the muscle fibers there is a slight infiltration with large mononuclear cells and lymphocytes

Except for a slight scattered granular calcification in the media and a very slight lymphocytic and mononuclear infiltration in the adventitia, the aorta is practically normal

The pulmonary artery shows slight thickening of the intima but it is nowhere sufficient to cause the slightest obstruction to the circulation. On the contrary even the smallest branches of the pulmonary artery appear to be dilated

In the lungs many of the bronchi contain masses consisting of an amorphous coagulum in which are embedded leukocytes, red cells and masses of bacteria. Many

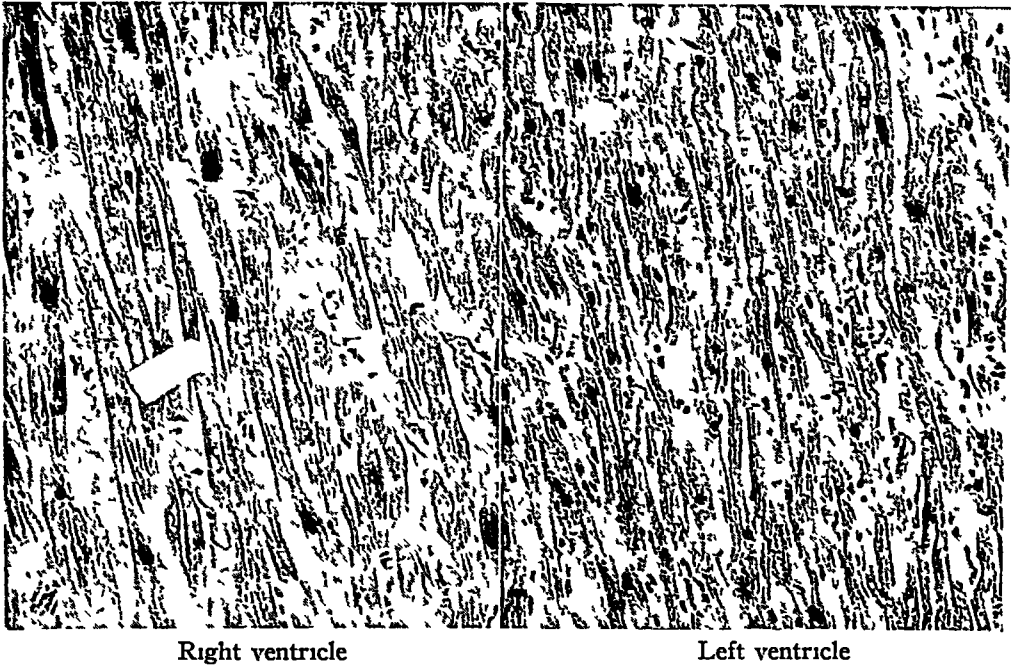


FIG 3 Sections of myocardium showing hypertrophy of muscle fibers in right ventricular wall (both photographs 160 X)

of the organisms are cocci in chains. Other bronchi are empty. In many sections the normal columnar epithelium is replaced by low stratified epithelium. The basement membrane in most of the bronchi is very thick and hyalinized (figure 4). There is slight to marked infiltration of the bronchial walls and peribronchial tissue with lymphocytes, plasma cells, and eosinophiles. Some of the bronchi are dilated and thin-walled, and show no inflammation. The smooth muscle of the bronchial walls is slightly hypertrophied. The mouths of some of the mucous glands are dilated, but there is no saccululation as described by Macdonald.

The alveoli are mostly empty, but in one section they contain finely granular precipitate indicating edema. In some areas they are dilated and the walls appear thin. There are several patches in which the alveoli are filled with an exudate of polymorphonuclear leukocytes.

Some of the larger branches of the pulmonary artery show moderate intimal thickening, due chiefly to an increase of fibrous tissue, but there are also pale areas suggesting deposits of lipid. A few lymphocytes and large mononuclear cells are present in the thickened intima. The media of these vessels is normal, and there is no infiltration of the adventitia or perivascular tissue. In spite of the intimal thickening there is no noticeable narrowing of the lumina of these vessels. The smaller arteries and arterioles are considerably dilated. Their walls appear thin and stretched, but otherwise normal. The lumina are empty. None of the vessels shows

thrombosis. Capillaries in the alveolar walls are not dilated, and there are very few "heart failure cells" and no other definite evidence of chronic passive congestion.

Except for a marked dilatation of the central veins of the lobules of the liver and the branches of the portal vein this organ is normal.

The spleen appears normal.

The glomeruli of the kidney are larger and more cellular than normal. The capillary endothelium and the epithelium covering the glomerular tufts are swollen. Many of the glomeruli are partly converted into hyaline material, some are completely hyalinized. Many of the capsular spaces contain small masses of hyalinized

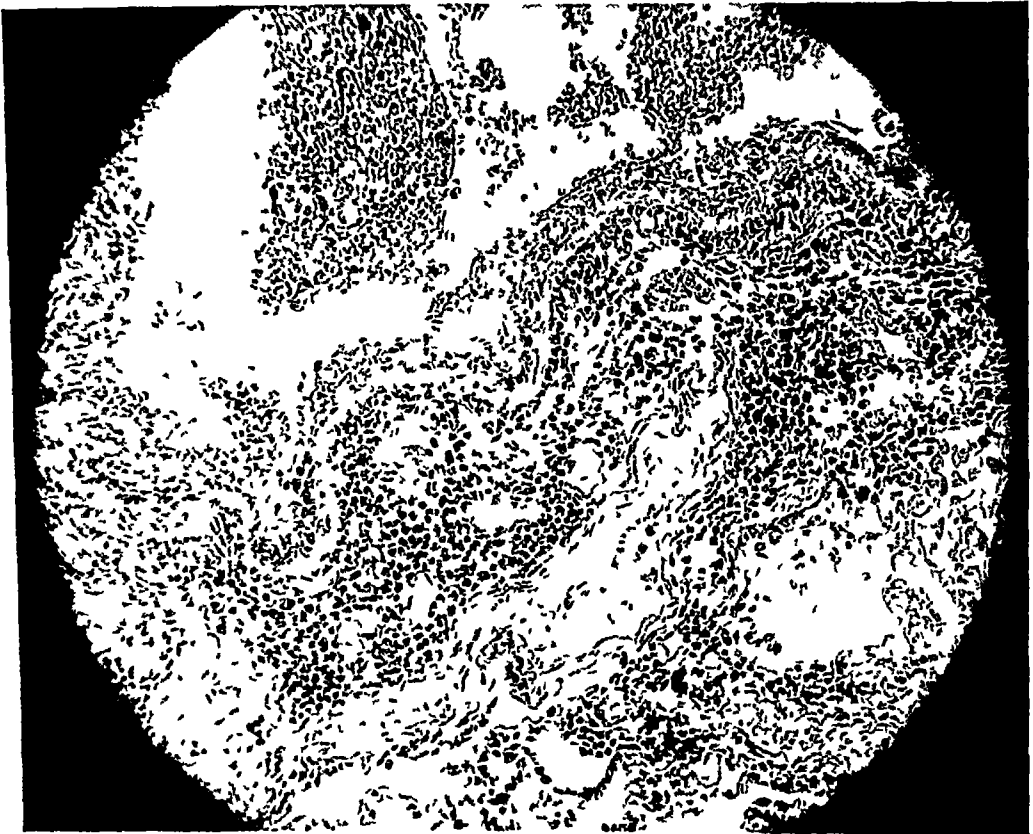


FIG. 4. Section of bronchial wall showing exudate in lumen, thickening and hyalinization of basement membrane, and cellular infiltration indicating chronic inflammation.

fibrin, a few contain small numbers of polymorphonuclear leukocytes, and some are filled with red corpuscles. Around many glomeruli the cells of the outer layer of Bowman's capsule are swollen, and frequently have proliferated to form typical epithelial crescents. Many capsular adhesions are noted. Some of the convoluted tubules are small, others are dilated and contain granular precipitate in some places mixed with red corpuscles and occasionally with polymorphonuclear leukocytes. A moderate number of small hyaline casts is present, especially in the collecting tubules. The interstitial connective tissue is slightly increased in amount, especially around the Bowman's capsules. The interstitial tissue is diffusely infiltrated with lymphocytes, plasma cells, large mononuclears and polymorphonuclear leukocytes. Some of the renal vessels show slight intimal thickening but the changes do not appear marked enough to be significant.

The bone marrow (figure 5) from the shaft of the femur is moderately congested and more cellular than normal but the hyperplasia is not marked, and adipose tissue is abundant. Cell types do not show any distinct variation from the normal.

The pathological features of this case may be summarized as follows. The heart shows hypertrophy of the right ventricle and a slight subacute myocarditis, which may possibly be related to a streptococcus infection in the respiratory tract. The slight sclerosis of the pulmonary artery is probably related to the increased pressure in the pulmonary circulation, but there is no evidence that this sclerosis itself is responsible for any obstruction in the circulation. The branches of the pulmonary arterial system are generally dilated. The sections of the lungs show all the evidence of chronic bronchitis and emphysema and the usual picture associated with bronchial asthma. An acute but not very extensive bronchopneumonia may have been a

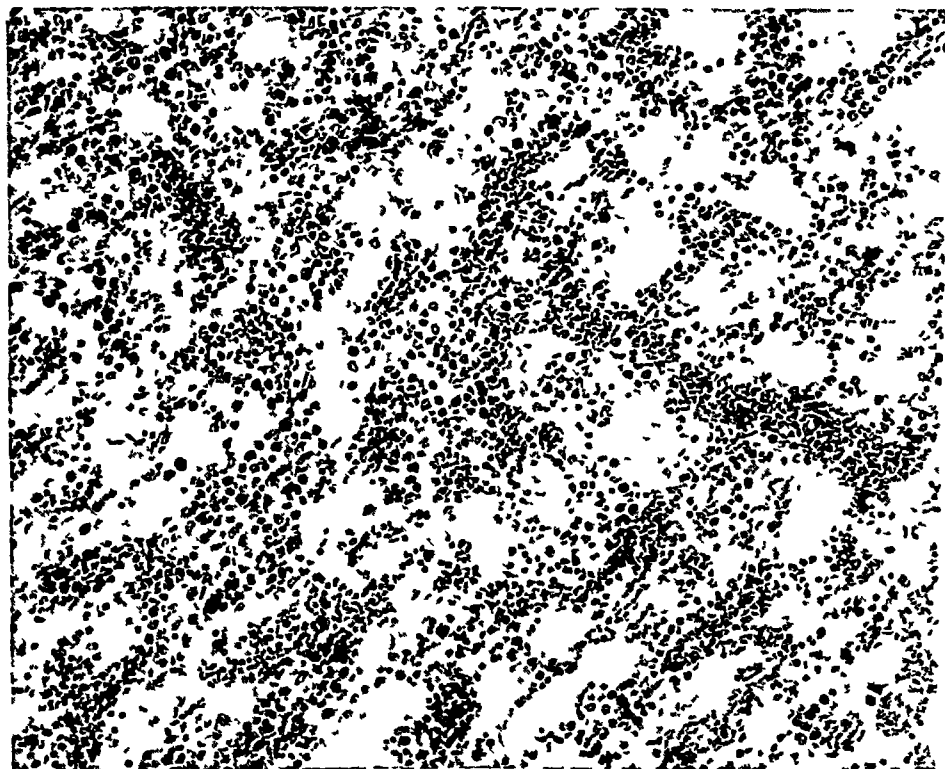


FIG 5 Section of bone marrow from middle of shaft of femur, showing moderate hyperplasia. The sinusoids are congested.

terminal condition. The kidneys show a very marked subacute glomerulonephritis. The viscera show no evidence of chronic passive congestion. Finally the bone marrow (figure 5) of the femur is more cellular than normal, but there is nothing like the marked hyperplasia which occurs in primary erythremia.

ANATOMIC DIAGNOSIS

Chronic adhesive pleurisy, acute bronchopneumonia, chronic bronchitis emphysema, slight hypertrophy of the left ventricle, marked hypertrophy of the right ventricle, dilatation of the pulmonary artery, slight pulmonary arteriosclerosis, subacute glomerulonephritis, moderate hyperplasia of the bone marrow.

GENERAL DISCUSSION

Current opinion holds that pulmonary arteriosclerosis is a frequent but not indispensable finding in the "black cardiac" (Warthin, Escudero,²³

L Ayerza, Arrillaga) The Argentinians use the terms "cardiacos negros" and "Ayerza's disease" almost synonymously with pulmonary arteriosclerosis. The arterial lesion may be primary and affect the smaller vessels or secondary and involve the larger branches of the pulmonary artery. Originally Abel Ayerza (1901) thought the primary lesion in the black cardiac was a wide-spread pulmonary fibrosis to which the right ventricular hypertrophy was secondary. Escudero first noted (1905) the significant association of pulmonary arteriosclerosis and later (1911) suggested that syphilis might be the cause of both the prodromal pulmonary symptoms and the subsequent arterial lesions. Warthin²⁴ is given great credit by the Spanish-Americans for demonstrating (1917) the *Spirocheta pallida* in the wall and sac of an aneurysm of the pulmonary artery, but the clinical picture in this case was not that of the "black cardiac". In a subsequent paper (1919) on "A Case of Ayerza's Disease" he was unable to demonstrate the spirochete but nevertheless was convinced by microscopic study that the lesions of the pulmonary artery were syphilitic. Arrillaga formerly believed that long-continued intoxication by alcohol, or chronic disease like syphilis, tuberculosis and malaria predisposed to the localization of sclerotic lesions in the pulmonary artery, especially when chronic pulmonary processes like asthma and emphysema by increasing peripheral resistance raise the pulmonary arterial tension. He now believes that the primary lesion is a syphilitic pulmonary arteriosclerosis. Bullrich²⁵ reports an extremely interesting case of the cure of a typical "black cardiac" by intense anti-syphilitic treatment. Arrillaga concurred in the diagnosis, which was well supported by electrocardiographic, radiologic and hematologic tests. It is quite clear that syphilis is frequently present in the "black cardiac", it is not clear whether the arterial lesion commonly found is syphilitic or not.

Marked obstruction of the lesser circulation by thickening of the arterial wall or thrombosis has a double effect, down-stream it leads to chronic anoxemia, the clinical expression of which is cyanosis, dyspnea and polycythemia, up-stream by increasing the work of the right ventricle it leads to hypertrophy and eventual failure of the right side of the heart.

Since gas exchange is dependent upon the integrity of the alveolar-capillary wall, the capillary bed is the critical point at which obstruction to the circulation makes itself felt. Reduction in the area of the capillary bed may be due to manifest obstruction in the main channels as by pulmonary thrombosis or pulmonary arteriosclerosis, it may be due to obstruction in the small vessels as by obliterative endarteritis, or finally it may be the result of less obvious but more direct interference as in the case of pathological processes which affect the alveolar-capillary wall itself. In all instances, as in the cyanotic group of congenital cardiac defects, a portion of the blood stream is shunted away from its designated oxygenating station. Anoxemia is the result of the diversion, increased pulmonary arterial tension and right ventricular hypertrophy are the results of the obstruction.

Pulmonary arteriosclerosis of slight degree only was found in our case.

It was not sufficient to produce obstruction. In fact, from the pulmonary valve to the arterioles the pulmonary artery and all its branches were dilated and this must have lightened somewhat the labors of the right ventricle. Yet this chamber of the heart was greatly hypertrophied. In our opinion this hypertrophy was due partly to the pulmonary condition, namely, chronic adhesive pleurisy, chronic bronchitis, bronchial asthma, emphysema and peribronchial pulmonary fibrosis, and partly to the strain of hard work at high altitude. The paper of Alexander, Lutten and Komitz²⁰ on the effect of chronic asthma and emphysema upon the heart has thrown much doubt upon the hitherto accepted idea that hypertrophy of the right ventricle is often found with bronchial asthma. These workers conclude that the heart in asthma is "largely enlarged and often comparatively small" and suggest that a probable increase in intrathoracic pressure may decrease the filling of the heart and so reduce its burden. In sharp contrast with this study of the heart in the living asthmatic is the recent report by Ian G. Macdonald²¹ on the pathological findings in eight cases of bronchial asthma collected from 3690 autopsies at the Hospital of the University of Michigan. In five of these cases death was due to cardiac failure during or following a paroxysm of bronchial asthma. Including the heart of a 13 year old girl the average thickness of the left ventricular wall in the eight cases was 18.25 millimeters, which may be compared with a normal average of 12.55 millimeters and a measurement in our case of 20 millimeters. The right ventricular wall in Macdonald's eight cases averaged 7.87 millimeters compared with a normal average of 3 to 4 millimeters and a measurement of 14 millimeters in our case. The right ventricular wall, writes Macdonald, was at least slightly thickened in every case.

The effects of emphysema, the inevitable complication of bronchial asthma, upon oxygenation and the pulmonary circulation are not easily measured but must be included in any appraisal of the influence of asthma upon the heart. In general they may be analyzed as follows: (1) A reduction in vital capacity, (2) an increase in the ratio of residual air to lung capacity, (3) a reduction in the area of the capillary bed, (4) a reduction in respiratory surface area, (5) increased tension in the lesser circulation, (6) a decrease in the assistance rendered by the thoracic and diaphragmatic movements to ventilation and to the pulmonary and general circulations. These changes lead inevitably to anoxemia and frequently to right ventricular hypertrophy.

The dilatation of the pulmonary artery and its branches may have represented the effort of the vascular system to accommodate itself to the increased blood volume (Brown and Giffin). In two cases of polycythemia vera Schreyer found the pulmonary artery much dilated and with walls only one-half as thick as normally. In neither case was the right ventricle hypertrophied. In our case, the hypertrophy of both the right auricle and the right ventricle and the dilatation of the pulmonary artery may be considered typical findings of pulmonary heart disease.

Brown and Giffin have studied renal function in eight cases of polycythemia vera. Albumin graded 1 to 3 was found in the urine in all, hyaline and granular casts in six, erythrocytes in one. The phenolsulphonphthalein elimination was slightly decreased in four cases and moderately decreased in two. They conclude that polycythemia vera exerts no marked deleterious effect directly on the kidney. Although Curschmann and Geisbock both report chronic degenerative changes in the kidneys, usually an extreme vascular fullness only is found. Turk says the renal changes are due to the "simultaneous presence of hyperemia and vascular dilatation". The glomerulonephritis in our case was probably due to a streptococcus infection of the bronchi, tonsils or sinuses. On one or two occasions, the sharp contrast between the condition of this man as he came down to Denver from camp in the high mountains and his condition two weeks later was strongly suggestive that dys-acclimatization was also an important cause of the albuminuria. Since the blood pressure was never high and examination of the blood never showed marked nitrogen retention the renal function was not seriously disturbed. Experimental work of Richards²⁸ and his co-workers has indicated a prompt appearance of albuminuria when the oxygen supply to the kidney is restricted. J. A. Campbell²⁹ has demonstrated degenerative and necrotic changes in both the liver and the kidney in certain animals for some time subjected to a low oxygen tension. Clinically, in both acute and chronic mountain sickness, evidences of serious renal embarrassment are often found. Oliguria with more or less albuminuria is commonly present, in the severe cases anuria may be found. Return to sea level brings about a remarkable diuresis within 24 hours, and usually complete disappearance of the albumin. Doubtless both the oliguria and the high cell volume (hematocrit) in the very severe cases reported by Monge are related to the gastrointestinal symptoms from which these patients often suffer. Nausea and vomiting restrict the intake of fluids and diarrhea further concentrates the blood. The red blood cells in the urine may have been due to the glomerulonephritis or to leakage from an over-filled vascular system.

The edema which became massive at the end was largely renal but partly cardiac. Alexander, Luten and Kountz included in their paper details of a postmortem examination of a chronic asthmatic who during life had dependent edema, dyspnea and cyanosis suggesting cardiac insufficiency. They found nothing unusual in the heart and therefore concluded that the edema in bronchial asthma might result from a retarded venous circulation. The increased blood viscosity in our patient must have contributed greatly to this effect.

The drop in the red cell count during the last few months of this man's life was due to three causes: (1) Residence at a lower altitude, (2) increase of plasma volume from cardio-renal edema, (3) subacute glomerulonephritis.

CONCLUSION

The combination of cyanosis, dyspnea, and polycythemia is the clinical expression of chronic anoxemia and the response of the bone marrow to the physiological stimulus of that anoxemia. When to this combination is added right ventricular hypertrophy, we have the syndrome of the "black cardiac" or the syndrome of Ayerza. Prolonged obstruction in the lesser circulation anywhere from the main divisions of the pulmonary artery to the pulmonary capillary bed may reproduce this clinical complex.

BIBLIOGRAPHY

- 1 WARTHIN, A. S. A case of Ayerza's disease, etc., *Contrib to Med and Biolog Res*, 1919, II, 1042-1059
- 2 MONGE, C. *Les erythremies de l'altitude*, 1929, Masson, Paris
- 3 ARRILLAGA, F. C. (a) *La arteritis pulmonar*, Buenos Aires, 1925, 8vo, pp 274, (b) *Esclerosis secundaria de la arteria pulmonar y su cuadro clínico (cardiacos negros)*, tesis, Buenos Aires, 1912
- 4 HARROP, G. A., JR. Polycythemia, *Medicine*, 1928, VII, 291-344
- 5 OSLER, W. Chronic cyanosis, with polycythemia and enlarged spleen a new clinical entity, *Am Jr Med Sci*, 1903, CXXVI, 187-201
- 6 ROWNTREE, L. G., and BROWN, G. E. The volume of the blood and plasma in health and disease, 1929, W. B. Saunders Co., Philadelphia
- 7 BROWN, G. E., and GIFFIN, H. Z. Studies of the vascular changes in cases of polycythemia vera, *Am Jr Med Sci*, 1926, CLXXI, 157-168
- 8 LEMON, W. S. A study of the effect of chronic pulmonary diseases on the volume and composition of the blood, *ANN INT MED*, 1929, III, 430-446
- 9 SMITH, H. P., BELT, A. E., ARNOLD, H. R., and CARRIER, E. B. Blood volume changes at high altitude, *Am Jr Physiol*, 1924-1925, LXXI, 395-412
- 10 DOUGLAS, C. G., HALDANE, J. S., HENDERSON, Y., and SCHNEIDER, E. C. Physiological observations on Pike's Peak, *Trans Roy Soc (Phila)*, 1913, CCIII-B, 231
- 11 JAQUET, A., and SUTER, F. Über die Veränderungen des Blutes im Hochgebirge, *Korresp Bl f Schweiz Arzte*, 1898, XXVIII, 104
- 12 GUILLEMARD, H., and MOOG, R. L'hyperglobulie des altitudes, *Compt rend de L'Acad des Sc*, Paris, 1906, CXLIII, 651
- 13 SMITH, L., and MCKISACK, H. L. On a case in which cyanosis and plethora occurred in association with adherent pericardium, *Trans Path Soc*, London, 1902, LIII, 136
- 14 WEBER, F. P., and DORNER, G. A case of congenital pulmonary stenosis with special consideration of the nature of the secondary blood changes, *Lancet*, 1911, I, 150
- 15 HALDANE, J. S. *Respiration*, 1922, Milford, London
- 16 BINGER, M. W. Anoxemia and polycythemia in chronic pulmonary disease, *Proc. Staff Meet*, Mayo Clinic, 1931, VI, 353
- 17 AYERZA, L., SOLARI, L. A., and BERCONSKY, I. Cyanose par hypoventilation alvéolaire chez un cardiaque noir d'Ayerza, *Arch d mal du coeur*, 1931, XXIV, 209-228
- 18 MEAKINS, J. C. Modern muscle physiology and circulatory failure, *ANN INT MED*, 1932, V, 506-513
- 19 BOOTHBY, W. M. Oxygen therapy, *Jr Am Med Assoc*, 1932, XCIV, 2026
- 20 BARCROFT, J. The respiratory function of the blood, Part I, *Lessons from high altitudes*, 1925, The University Press, Cambridge
- 21 KATZ, L. N., and LONG, C. N. H. Lactic acid in mammalian cardiac muscle—Part I The stimulation maximum, *Proc Roy Soc*, Ser B, 1925-26, XCV, 8-20
- 22 MINOT, G. R., and BUCKMAN, T. E. Erythremia (polycythemia rubra vera), *Am Jr Med Sci*, 1923, CLXXI, 469

- 23 ESCUDERO, P Enfermadad de Ayerza, Rev de la Soc de Med Int, 1925 (Nov), T I, 701
- 24 WARTHIN, A S Syphilis of the pulmonary artery syphilitic aneurysm of the left upper division demonstration of Spirocheta pallida in wall of artery and aneurysmal sac, Am Jr Syph, 1917, 1, 693
- 25 BULLRICH, R A Observacion de un "cardiaco negro" curado (Notes on the recovery of a "black cardiac"), Rev Med Latino-Amer, 1926, an xi, 1689
- 26 ALEXANDER, H L, LUTEN, D, and KOUNTZ, W B Effects on the heart of longstanding bronchial asthma, Jr Am Med Assoc, 1927, lxxxviii, 882-884
- 27 MACDONALD, I G The local and constitutional pathology of bronchial asthma, ANN INT MED, 1932, vi, 253-277
- 28 RICHARDS, A N The function of the kidney, Colo Med, 1926, xxiii, 11-14
- 29 CAMPBELL, J A Prolonged alterations in oxygen pressure in the inspired air, Jr Physiol, 1926-1927, lxiii, 325

A STANDARD TEST FOR MEASURING THE VARIABILITY OF BLOOD PRESSURE: ITS SIGNIFICANCE AS AN INDEX OF THE PREHYPERTENSIVE STATE *

By EDGAR A. HINES, JR., M.D., and GEORGE E. BROWN, M.D., F.A.C.P.,
Rochester, Minnesota

IN HEALTH there is a balance of the various divisions of the autonomic nervous system that varies with the normal physiologic demands. It is likely that phylogenetic and anatomic factors, as well as the functional requirements of the organs have determined certain thresholds of activity of the sympathetic control of the different organs. The maintenance of cardiac rate at about 70 beats a minute, the control of surface temperature within a certain range, the activity of the sweat glands, and the control of the arterial blood pressure, illustrate these physiologic balances. Overactivity of the sympathetic and parasympathetic components of the autonomic nervous system frequently affects or produces symptoms or syndromes so distinctive as to be recognized as clinical entities, such as irritable heart or effort syndrome, or, when affecting the vasomotor nerves of the peripheral vessels, as vasospastic or vasodilating disturbances which are familiar clinical conditions. Neurogenic disturbances of the sweat glands are observed as forms of hyperhidrosis and hypohidrosis. If imbalance of the vasomotor system involves a sufficient amount of the vascular bed, alterations in the systemic blood pressure follow.

Postural hypotension represents disturbance of the sympathetic system expressed in the blood pressure, and is probably due to disease of the sympathetic nerve endings. Essential hypertension could be explained on the basis of vasomotor imbalance, with an abnormal degree of vasoconstriction. The basis of the overactivity of the different portions of the autonomic nervous system is unknown, it may be constitutional or biologic. Some disturbances of the sympathetic balance expressed as visceral neuroses are common among subjects of the constitutionally inadequate type. Psychic, emotional, or traumatic upsets may be the activating factors. The hormones that stimulate the sympathetic nerves (from the thyroid and suprarenal glands) play a part by affecting the nervous tonus. Subjects with essential hypertension are usually constitutionally adequate types, exhibiting psychic hyperirritability, with evidence of increased influence of the sympathetic nervous system, and less of the parasympathetic nervous system. The question involved in the pathogenesis of essential hypertension is whether the central or peripheral mechanism is at fault. Is there a hypersensitive vasomotor center, or are the effector tissues, the sympathetic

* Read before The American College of Physicians, Montreal February 10, 1933
From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota

nerves, the vascular tissue, or the endocrine functions responsible? Monakow and others have postulated that the vasomotor centers are hyperirritable and set at a higher level. Analogies exist in disturbances of the thermoregulatory centers in neurogenic fevers. More recent experiments by Raab throw added light on this point. He found that in cases of essential hypertension inhalation of carbon dioxide caused a rise in blood pressure several times greater than that of normal subjects. Interestingly, normal responses were found in hypertension in nephritis.

A CONCEPT OF HYPERTENSION

There is (a) a primary or major factor, consisting of a hyperreactive sympathetic vasomotor mechanism based on constitutional abnormality or imbalance, and (b) a subsidiary factor of "wear and tear" from various environmental agents which modify or accentuate or activate the constitutional factor (table 1). It is possible that this hyperreactive mechanism

TABLE I

Etiology of Essential Hypertension

- | | |
|----|--|
| I | Constitutional or X factor, expressed as
Hypersensitive vasomotor center
Abnormal reactor mechanism
Arteriolar tissue
Sympathetic nerve endings
Endocrine |
| II | Subsidiary or accelerating factors of wear and tear
Environmental agents
Toxic or infectious effects |

can be acquired. The aboriginal African negro does not have hypertension, but among the first and second generations of transplanted negroes, hypertension is common, and often more severe than among the native white subjects.

If there is a biologic basis which determines the subsequent development of hypertension, it should be possible theoretically to recognize this abnormality in the individual, from birth or perhaps from puberty, years before the onset of clinical hypertension. To establish this point, it was necessary to devise some type of standard stimulus whereby the pattern of reaction of the vasomotor system could be determined.

THE COLD STIMULATION TEST

The test as employed consists in placing the subject in a recumbent position for fifteen minutes, or until the blood pressure has attained or approximated the basal level. In cases of hypertension, as long as forty-five minutes may be required. With the cuff placed on one arm, the opposite hand is placed in ice water, 4° to 5° C, the blood pressure is taken at the end of thirty seconds and again at the end of sixty seconds. The hand is removed from the ice water and readings are taken every two minutes until the blood pressure returns to its previous basal level. The highest

reading obtained is recorded as a measure of the response. Except for a small group of subjects with hypertension the blood pressure returns to the basal level within two minutes after the hand is removed from the ice water. This reaction is independent of any significant changes in the pulse rate. There is response in both systolic and diastolic pressures, but somewhat less and more variable in the latter.

The Basis of the Reaction It is likely that the response to cold has purely a neurogenic reflex basis, because of the speed of the reaction, which is too rapid for the intervention of any known hormonal or chemical factor. A tourniquet producing stasis of the flow of blood in the arm that is immersed fails to inhibit the reaction.

Data Two hundred and thirty subjects have been observed. They included 69 normal subjects, 41 subjects with diseases other than of vascular type, 26 patients with localized forms of vascular disease, 76 subjects with hypertension, and 18 subjects without hypertension who seemed to be normal except that they gave abnormal reactions. The subjects were fairly equally divided as to sex.

The subjects with hypertension were grouped (on the basis of presence or absence of demonstrable organic changes in the retinal arterioles) as demonstrating organic or preorganic types of the disease. Table 2 is a

TABLE II
Responses of Blood Pressure to Cold Test

Type	Subject		Mean rise in pressure	
	Num- ber	Age, years	Systolic	Diastolic
Normal	69	15-55	8.62 \pm 0.181	8.14 \pm 0.182
Hyperreactive, "normal"	18	17-40	29.33 \pm 1.21	23.33 \pm 1.05
Hypertension				
Organic	49	24-64	36.68 \pm 1.27	24.38 \pm 0.978
Preorganic	21	24-64	37.15 \pm 2.07	25.04 \pm 1.52
Arteriosclerosis with hypertension	6	68-91	35.00 \pm 4.99	20.08 \pm 0.735
Various diseases except vascular	41	18-45	8.15 \pm 0.277	7.27 \pm 0.192
Vascular diseases without hypertension	26	22-82	9.77 \pm 0.477	8.47 \pm 0.353

summary of the data obtained concerning all subjects studied. On the basis of the response of the blood pressure to cold, there were two well-defined groups. Group 1 includes subjects with minimal response to cold stimulation, and group 2 those whose response is two or more times greater. In group 1 are the normal subjects and those with other diseases than hypertension. The average response was 8.8 mm of mercury for the systolic rise and 7.93 mm for the diastolic rise. The range was 5 to 15 mm systolic and 5 to 12 mm diastolic pressure. Those subjects with increases as high as 15 mm of mercury have been considered arbitrarily as giving maximal normal reactions. In group 2 are all patients with levels of blood pressure sufficiently elevated to cause them to be designated as having essential hypertension, and the 18 young, healthy adults of both sexes who had normal

blood pressures and no other symptoms indicative of hypertension, but whose reactions were abnormal. The mean values for the response in blood pressure were 34.5 mm of mercury systolic and 23.2 mm of mercury diastolic. The range was from 20 to 90 mm in systolic pressure and from 15 to 65 mm in diastolic pressure (figure 1). Ninety-seven per cent of

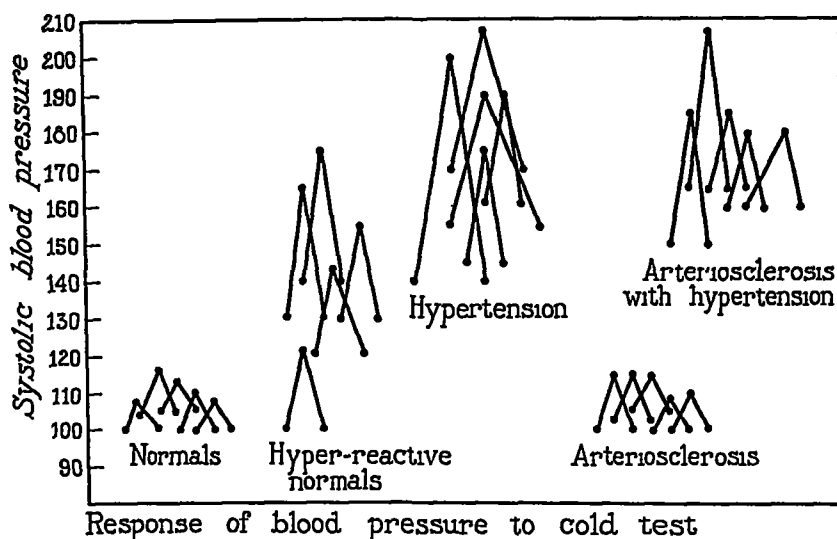


FIG 1 Response of systolic blood pressure to cold test

the subjects with hypertension gave a minimal response in systolic and diastolic pressure greater than the maximal response of any normal subject in group 1. With the exception of two subjects, the responses in group 2 were two or more times greater than in group 1. The two subjects whose responses were not greater than normal had the organic changes and the high fixed levels of blood pressure of the malignant form of hypertension. Basal levels were not attainable. There was no significant difference in the response in blood pressures between the preorganic and the organic forms of hypertension. In the group with hypertension there was significant correlation between the basal levels and the magnitude of the response in the systolic and diastolic pressures.

Constancy of the Reaction Repetition of the test at short and at long intervals showed a constancy of the reaction. No conditioning effects were noted under fairly parallel conditions.

Effects of Age We have insufficient data to allow us to state the effects of age on the reactions to cold. Among older subjects, with high grades of arteriosclerosis, responses were normal. Among older subjects with mild forms of hypertension of the arteriosclerotic type, responses were exaggerated. Further investigation of the effect of age, especially as regards infants and subjects in the later decades of life, should be carried out.

Effect of Rest Hourly observations of blood pressure have shown that controlled mental and physical rest has a depressor effect on both the magnitude of the fluctuations and on the mean levels of systolic and diastolic pressure in cases of essential hypertension. Short periods of rest (twenty-

four to forty-eight hours) had no significant effect on the response of the blood pressure to stimulation by cold. Long periods of rest (one to two weeks) might significantly diminish the vasomotor reaction. With resumption of activity the reaction returned to its previous level.

Effect of Drugs Derivatives of barbituric acid have a depressing effect on the reaction to cold. Sodium amytal in doses of 3 to 6 grains (0.2 to 0.4 gm) reduced the magnitude of the reaction from 50 to 100 per cent, and the reduction endured from three to twelve hours. The effect on the blood pressure could be obtained without objective slowing of the psychic reactions (figure 2). Bromides were much less effective. Bismuth sub-

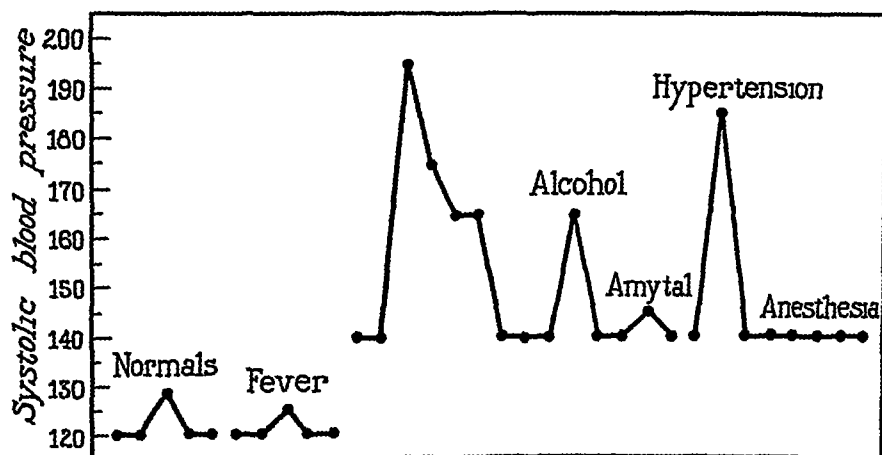


FIG 2 Effects of different agents on the blood pressure response to cold test

nitrate given in doses of 30 grains (2 gm) daily for periods as long as two weeks, had no effect on the reaction. Calcium chloride given intravenously in doses of $7\frac{1}{2}$ grains (0.5 gm) gave an increased response to the cold test, and a marked delay (thirty to sixty minutes) in the return of the blood pressure to basal levels. Ethyl alcohol, given by mouth in doses of 0.5 cc for each kilogram of body weight, reduced the response to cold, the average decrease was 40 per cent. The duration of the decrease was from two to twelve hours. The depressor effect of alcohol was also demonstrable in the mean levels of systolic and diastolic pressure.

Effect of Anesthesia General anesthesia caused complete obliteration of the response. Lumbar anesthesia produced a diminishing effect, roughly proportionate to the level of the anesthesia, and to the level of the systemic blood pressure. With anesthesia to the level of the nipple line, the vasomotor response was less than normal. With gradual lowering of the level of anesthesia, the vasomotor reaction increased in magnitude to the pre-anesthetic level (figure 3).

Effect of Quantitative Reduction of the Sympathetic Nervous System Following either cervicothoracic or lumbar ganglionectomy, or both, on man with normal blood pressures no change was found in the vasomotor re-

renalectomy on the dog, with life maintained by injections of cortical extract (Kendall), there was no significant decrease in the response of the blood pressure to the stimulus by cold. If the cortical extract was withheld, the vasomotor response to cold was maintained until critical levels of blood pressure supervened.

COMMENT

The primary etiologic factor in essential hypertension is believed to be some constitutional abnormality. The significant question in pathogenesis is whether this abnormality is of central or peripheral origin. Experimental work on the animal, with progressive reduction of the sympathetic vasomotor nerves, shows that the vasomotor reactions decrease in magnitude as larger regions of vasomotor control are eliminated. This points to a central origin. It is likely that in subjects with essential hypertension the vasomotor centers react excessively to stimuli which in the normal subject produce minimal response. A parallel is seen in Raynaud's disease, in which thermal stimulation (cold) causes excessive constriction of the peripheral vessels. In the early uncomplicated types of Raynaud's disease, the evidence indicates hypersensitively reacting vasomotor centers. In most cases of Raynaud's disease the blood pressure responses to cold are in the maximal range for normal subjects.

If the hyperreactability in essential hypertension is due to a biologic constitutional defect, theoretically its existence should be demonstrable in early life. The reaction to cold is probably of definite value in establishing this point. A few subjects have been found to react excessively before puberty. Many children of all ages should be studied and the results correlated with the type of vasomotor reactions of the parents. In this way the hereditary or familial factor could probably be determined. Our study has shown that so-called normal subjects can be grouped as hyporeactors and hyperreactors. It remains to determine the significance of the hyperreaction. There is no conclusive proof as yet that the "normal" subjects who react excessively to cold will eventually have hypertension. The belief that they may be so afflicted in the future is based on the following: (1) in the immediate ancestry of more than 75 per cent of the subjects with hyperreactions there was a history of hypertension or of apoplectic death, this figure is undoubtedly understated, for deaths from cardiac or renal causes in the families were not included, and (2) at least 98 per cent of subjects with essential hypertension have hyperreactive responses. The final proof will rest on follow-up studies carried out over a period of years.

One may question whether the hyperreactive subjects react excessively to other stimuli as well as to local application of cold. There is close parallelism, as is shown in figure 5. It is probable that all sensory and psychic stimuli produce excessive reactions in the hyperreactive subject. None has been found as effective as local application of cold. We have not discovered other diseases than essential hypertension in which there were excessive

reactions, exceptions may be found in hyperthyroidism. In cases of fever there may be lowered responses. Two subjects with Addison's disease had normal reactions. Eight subjects with intermittent systolic hypertension, associated with tachycardia recognized as "effort syndrome," have had normal reactions. In two cases of aortic insufficiency with a secondary form of systolic hypertension, normal reactions were found. In two cases of nephritis with secondary hypertension reactions were normal.

We believe that hyperreactions of the systemic blood pressure are of

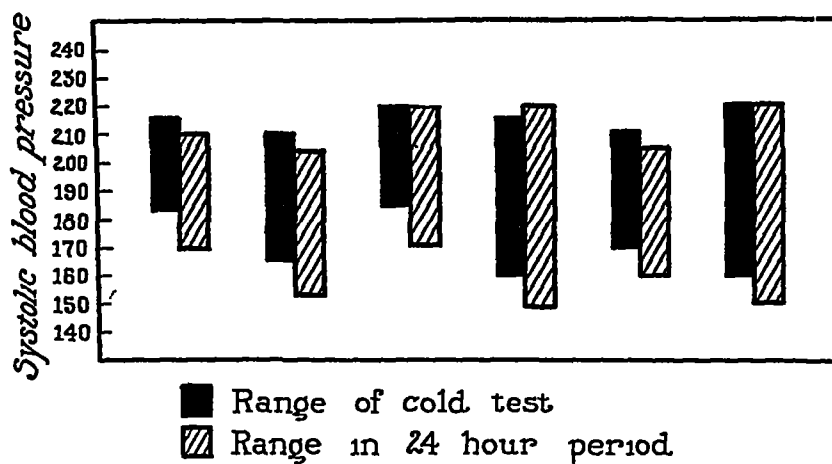


FIG 5 Correlation of effects on the blood pressure of environmental stimuli, and stimulation by cold

great importance in determining the vascular longevity. During the ascending period of life there is excessive intermittent tonicity of the smaller arteries associated with abnormal intermittent intravascular stress and strain. Pathologic wearing of the vascular tissue could be postulated. The first response to this excessive work on the part of the musculature of the arterioles is analogous to that occurring in the heart, that is, hypertrophy, a physiologic response. With mesial hypertrophy, true organic narrowing of the arteriolar lumen exists. With this organic narrowing of the distal arterioles, rising levels in systolic and diastolic blood pressure would be expected. At this stage the condition is recognized as clinical hypertension, probably an irreversible condition, as indicated by the lack of response to therapeutic endeavors.

The value of diagnosing hypertension in the functional, or preorganic stage of the disease is obvious. If therapeutic measures are to be of avail, they must be instituted before organic deterioration has developed. We assume that the excessive reactions are the precursors and have etiologic significance in producing the state of hypertension. If this assumption is granted, then the therapeutic viewpoint is clarified. The factors of wear and tear assume great significance and the effect of depressing the vasomotor reactions should be salutary. Regulation of occupational and avocational activity is important. A large field of experimental therapeutics is opened. Our work has just touched this interesting phase of the subject. Enough

has been done to give some hope that adequate measures of control, either medical or surgical, of the vasomotor irritability will be available in the future

SUMMARY

There is impressive evidence to indicate that certain subjects have a constitutional or biologic abnormality which leads to the development of essential hypertension. Demonstration of this potentiality should be possible theoretically, years before the onset of clinical degrees of high blood pressure. Subjects can be grouped as those with minimal and those with excessive responses of the systemic blood pressure to sensory and psychic stimulation. A standard test has been devised which determines this response. There is some evidence that the so-called normal subjects who exhibit this hyperreactivity will eventually suffer from hypertension unless development of this condition is forestalled.

At least 98 per cent of all subjects with hypertension of the essential form exhibit excessive reaction to local cold. Subjects with other diseases have normal or minimal reactions*. The cold test is useful in determining the efficacy of therapeutic measures to control the vasomotor irritability.

BIBLIOGRAPHY

- CRAIG, W. M., and BROWN, G. E. Experiments on the control of blood pressure by operation on the sympathetic nervous system, *Proc. Staff Meet., Mayo Clinic*, 1932, vii, 61-64.
- DONNISON, C. P. Blood pressure in the African native, its bearing upon etiology of hyperpiesia and arteriosclerosis, *Lancet*, 1929, i, 6-7.
- VON MONAKOW, P. Blutdrucksteigerung und Niere, *Deutsch Arch. f. klin. Med.*, 1920, cxxxiii, 129-152.
- MUELLER, S. C., and BROWN, G. E. Hourly rhythms in blood pressure in persons with normal and elevated pressures, *Ann. Int. Med.*, 1930, iii, 1190-1200.
- PATEK, A., and WEISS, S. The tonus of the autonomic nervous system in arterial hypertension, *New Eng. J. Med.*, 1931, ccv, 330-334.
- RAAB, W. Funktionsprüfung des zentralen Vasomotorenapparates in verschiedenen Lebensaltern, *Ztschr. f. klin. Med.*, 1931, cxviii, 618-629.
- SCHWAB, E. H., and SCHULZE, V. E. The incidence of heart disease and of the etiological types in a southern dispensary, *Am. Heart J.*, 1931, vii, 223-234.

* Briggs and Oertling (*Minnesota Med.*, 1933, xvi, 481-486) have confirmed our studies on the cold stimulating test. They found hypertensive reactions in eight subjects with syphilis of the central nervous system. Their observation is important and needs further study.

THE DIAGNOSIS AND MEDICAL TREATMENT OF ANGINA PECTORIS*

By PAUL D WHITE, M D , F A C P ,

Boston, Massachusetts

ANGINA pectoris is one of the most important and interesting conditions that we meet in the practice of medicine today. It has become increasingly so during our own generation and at present is a great and pressing challenge to us all. Our much vaunted civilization of but a few years ago has been receiving many rude shocks, and to these we may add the seemingly justified accusation that it has been responsible for much of the apparent increase in angina pectoris in our day. Certainly such apparent increase cannot be ascribed wholly to better diagnosis since our forebears for over one hundred years have known this condition well, as you will note if you read the textbooks of medicine throughout the last century. Angina pectoris is the cause today of a great deal of the disability and of many of the deaths in a community like Boston, for instance. Our own profession is riddled with it. During 1931 the deaths of a few less than 3000 physicians of the United States were recorded in the *Journal of the American Medical Association*. The causes of death were not reported in every case but in over 1000 heart disease was listed as the cause, leading the second most common cause, cerebral hemorrhage, by just 700. Heart disease occurred in 1065 and cerebral hemorrhage in 365. Pneumonia was third with 312. Tuberculosis was far down the list with only 65 deaths. The type of heart disease was specified in less than half the cases but in those so classified one-third (114) were reported as having died of angina pectoris, the other two-thirds being diagnosed as endocarditis or myocarditis save for seven cases of pericarditis. It is certain that many more cases of angina pectoris existed among those unclassified and quite probably also among those labelled simply "myocarditis". In the report of a single week, of 47 deaths in the medical profession with causes diagnosed, the heart was held responsible in 21, with angina pectoris and coronary thrombosis definitely diagnosed in eight of these. The misfortune is that most of these men were under 70 years of age, of the 21 cardiac cases only six were 70 or over, there were four in the forties and six in the fifties. It is evident that we must do something about the prevention of this dread disease, and to that most important phase of the subject I shall return at the end of this paper. It is my province now to discuss mainly the diagnosis and medical treatment of angina pectoris.

* Presented before the American College of Physicians, Montreal, Canada, February 10 1933

RECOGNITION OF ANGINA PECTORIS

At the very outset the prime need is to recognize angina pectoris when we meet it and not to mistake other conditions for it. This task is generally an easy one, but errors due to carelessness are not infrequent. Let us begin with the definition and if we accept this definition, as I am confident we all do, we should not be troubled by the confusion that has occasionally, nay frequently, arisen in the past as to what is and what is not angina pectoris. Following Heberden who invented the expression, we should consider angina pectoris to mean a strangling or pressing sensation (not a stabbing pain or an ache) under the sternum occurring paroxysmally as the result of exertion, excitement, or other stimulus, and subsiding within a few minutes under the influence of rest or of nitrites. The only exceptions to this rule that may be allowed are the infrequent instances of *similar sensations occurring under the same circumstances* but in other parts of the chest in front or in either arm with or without radiation to the substernal region. Almost the rarest of the sites of true angina pectoris is the precordium itself in the region of the cardiac apex, that is, in the left breast. Radiation of the substernal oppression to left or to right, or to both sides, across the chest, towards or into the axillae is common, but much more so on the left side. Radiation to the left upper arm is frequent, to the left lower arm less common, and to the left hand and fingers relatively infrequent. Radiation to both arms occurs occasionally but to the right arm alone only rarely, although I have met an instance of an oppressive sensation limited to the right wrist, the cause of which was coronary disease. Radiation to the neck in the middle or on either side is infrequently encountered, to the jaws still less often, and to the back very rarely. I cannot recall a single instance in which the sensation radiated downwards into the abdomen or legs, although it may sometimes start in the epigastrium and penetrate upward under the sternum. As a rule the more severe the substernal oppression the more extensive the radiation, but there are frequent exceptions to this rule, and in some cases a very severe strangling sensation remains closely located in a small area under the middle of the sternum. When radiation does occur, the sense of oppression becomes modified to a burning, tingling, or numb feeling the further it radiates. Finally, it should be observed that among the stimuli that may produce angina pectoris there is in rare cases paroxysmal tachycardia or paroxysmal auricular fibrillation with rapid ventricular rate, the oppression in the form of the so-called status anginosus persisting while the tachycardia persists, just as it would do if there were persistence of other factors like exercise or excitement, this association of angina pectoris with paroxysmal tachycardia or paroxysmal auricular fibrillation has been recently called to attention because of the likelihood of confusing it with coronary thrombosis. The middle-aged or elderly male is most commonly the victim of angina pectoris, usually following much strenuous living.

Symptoms other than the substernal oppression, that have sometimes

been referred to as a part of angina pectoris are a sense of impending dissolution and faintness. Neither of these has been at all a common accompaniment of angina pectoris in my experience. Actual syncope (syncope anginosa) is rare. *Angina pectoris sine dolore*, a paradox in itself, is a term that has been used to describe feelings or symptoms that are assumed to occur as the result of acute coronary insufficiency in the place of the characteristic oppression or its variations. The term is very unsatisfactory and confusing and should be dropped. In contrast to coronary thrombosis which may be painless angina pectoris is a symptom and if that symptom is absent we cannot call other symptoms such as giddiness or an all-gone feeling angina pectoris even though coronary disease is present. When syncope complicates angina pectoris the oppressive feeling comes first.

TYPES AND CAUSES OF ANGINA PECTORIS

The fundamental types or causes of angina pectoris may be briefly considered now. Although the last word has as yet by no means been said with reference to the pathogenesis or mechanism of angina pectoris, we have advanced far enough to have a much clearer idea of the situation than was possible a generation ago when the controversy was at its height between those who supported the aortic origin of angina pectoris and those who supported its coronary origin. Four weighty arguments that have almost conclusively proved that the symptom is due to coronary insufficiency are first, that angina pectoris and proved coronary occlusion give the same kind and location of pain, second, that angina pectoris is often complicated by coronary thrombosis or indeed may appear for the first time after coronary thrombosis, third, that those cases of luetic aortitis with narrowing of the mouths of the coronary arteries are the ones that show angina pectoris while those cases of luetic aortitis who fail to show coronary mouth involvement even though the aortic lesions may be much more extensive, perhaps with actual aneurysmal sacs, do not have angina pectoris, and fourth, that constriction of the coronary artery in the dog produces pain while distension of the aorta does not. Thus we start with the premise that angina pectoris is caused by temporary coronary insufficiency. Equally important and even more conclusive is the evidence that the symptom occurs most readily in individuals with nervous hypersensitivity. It is practically unknown in lethargic persons and in full-blooded negroes, no matter how much coronary disease may be present in them. This very fact accounts for one of our greatest difficulties in the diagnosis of angina pectoris, the persons who are apt to have symptoms of various sorts easily produced are very likely to have angina pectoris also, although often the relatively sheltered lives that many of these individuals lead doubtless protect them from the strains that usually precipitate angina pectoris. With these introductory remarks we may attempt a simple classification of the types of angina pectoris as follows; the first two groups are quite certain, the last three probable or possible:

- 1 Coronary arterial sclerosis. A loss of elasticity with or without

much calcification and narrowing of the coronary arteries is the most common lesion in angina pectoris. In such cases the pain is doubtless induced by the improper functioning of the coronary circulation when there is extra demand on the myocardium, the myocardium in its turn is often thickened as the result of chronic hypertension or other strain and so requires more blood than before. The predisposing factors which impose the extra load are mainly, exertion, excitement, and eating, but include also anemia and tachycardia, the latter induced by thyrotoxicosis or occurring paroxysmally.

2 Coronary mouth occlusion by luetic aortitis or in a very rare case by ball valve obstruction from vegetations on the aortic valve may cause angina pectoris with such provocation as outlined under coronary sclerosis or indeed with less provocation.

3 Coronary arterial vasoconstriction, a vascular spasm, has been suggested as an occasional or frequent cause of angina pectoris, perhaps in the smaller vessels superimposed on sclerosis of the larger trunks. It has not been proved but may help to explain the attacks of angina pectoris occurring in hypersensitive individuals who suffer from hypertensive storms with relief of the angina pectoris on such occasions not directly related in time to the drop in blood pressure. However, in such cases further factors like aortic regurgitation or thyrotoxicosis may be present, and always or almost always structural changes in the coronary arteries themselves.

4 Marked aortic regurgitation and marked aortic stenosis have been found in a few cases of angina pectoris with no evidence of coronary disease clinically, but as yet there has not been clear postmortem evidence that the coronaries or their mouths are entirely normal. Also it has been in a part of this very group consisting of young people with marked aortic regurgitation that angina pectoris has occurred with hypertensive storms perhaps attended by coronary vasoconstriction. It is possible that, but open to some question whether, the diminished coronary blood flow that exists with marked aortic regurgitation or marked aortic stenosis can be sufficient basis for angina pectoris of effort.

5 Finally, we have recently encountered an infant who on such exertion as taking its milk would grow pale and cry out as if in pain and who after death from collapse at the age of four months showed the rare anomaly of malposition of the left coronary artery which arose from the pulmonary artery instead of the aorta. The electrocardiogram of this child showed typical coronary T-waves. The heart was enlarged and before death we had made a tentative diagnosis of congenital idiopathic hypertrophy.

In concluding these comments concerning the types of angina pectoris it should be added that certain conditions like severe anemia and thyrotoxicosis favor the onset of angina pectoris but do not cause it in a perfectly sound heart so far as we are aware. Extremely rare cases in which pressure on the coronaries from without gives rise to pain have been referred to as possible but I have not myself encountered any.

DIAGNOSIS OF ANGINA PECTORIS

The diagnosis of angina pectoris is wholly dependent on the patient's history unless one happens to observe a typical attack and note its relief by rest or nitrites. The sensation of the patient is the entire clue, all else is merely suggestive or corroborative of the diagnosis of coronary disease. Since it is obvious that this is so and since the diagnosis is a most important one, it behooves every one of us to take personally the detailed history given by the patient himself, and not to delegate the history taking to a relatively untrained medical student, assistant, or secretary. It is far better to delegate the physical examination than the history if for any exceptional reason the entire examination cannot be made by oneself. It is failure to observe this simple precaution of taking a careful detailed history of symptoms that has caused most of the mistakes of omission or commission in the diagnosis of angina pectoris. It is probably neither wise nor conclusive to give epinephrine as a diagnostic test.

There may or may not be complications with angina pectoris. The commonest are hypertension, cardiac enlargement, coronary thrombosis, and nervousness. Less common, but not infrequent, are aortic valvular disease, luetic aortitis, diabetes, and well marked generalized arteriosclerosis. Rare are congestive failure, auricular fibrillation, and mitral valvular disease. About one-fifth of all the cases show no abnormalities of the circulation on physical examination, roentgen-ray study, or electrocardiography. A few show no abnormalities except for intraventricular block or coronary T-waves in the electrocardiogram, these are common enough to make it wise to take electrocardiograms of men or women over 40 years old in all insurance examinations for large sums. A few instances have been recorded of transient changes in the electrocardiogram during attacks of angina pectoris, the opportunity to obtain such records is, however, infrequent and the finding is not a constant one.

The differential diagnosis of angina pectoris is generally a simple matter. This symptom should not be confused with the dull prolonged heartache or sharp stabbing knife-like or "pins and needles" pains of neurocirculatory asthenia or of big pounding hearts in nervous persons, even though such pain may be referred occasionally to the shoulder or down the left arm as a numbness. It is this kind of pain that is most often called pseudo- or false or secondary angina pectoris, such terminology is misleading. These aching or stabbing pains are a variety of *dolor pectoris* but not of *angina pectoris* as Heberden himself clearly recognized. In fact, angina pectoris is often described by the victim as not being pain at all, while the stabbing and aching sensations are always described as pain or *dolor*. There are four clues to the differentiation of these pains, which are largely of nervous origin, from angina pectoris: (1) their site (left breast), (2) their character (described above), (3) sensitiveness of the left breast to touch or pressure, and (4) other symptoms of neurocirculatory asthenia like sighing, faintness, and exhaustion. Angina pectoris itself may be slight or severe, but

it is always angina pectoris and not pseudo-angina pectoris. It is, however, important to remember that both angina pectoris and neurocirculatory asthenia may coexist in the same patient, the unravelling of such a case is of great interest and importance.

The next most common confusion in the differential diagnosis in the past has been between angina pectoris and coronary thrombosis. Although the clear separation clinically has been made only in the past decade, it is now easy except for rare borderline cases which need further study. The pain of coronary thrombosis is exactly like that of angina pectoris except that it is much more prolonged, lasting hours instead of minutes, and often, but not always, it is more severe.

So-called aortic pain probably occurs only when the aortic wall is seriously involved, and then it is quite likely to be due as much, or more, to the result of pressure of the dilated aorta, especially if there is a saccular aneurysm, on adjacent structures as to the lesions in the aortic wall itself. True aortic pain in clear cut cases is quite different from angina pectoris. It consists of a prolonged heavy ache, sometimes likened to a throbbing toothache, and often lasting hours or days at a time, unrelieved by nitrites and at times requiring morphine repeatedly, or paravertebral alcohol injection. It is commonly located in the region of the upper sternum and base of the neck especially to the right of the midline and often in the right shoulder or arm also, probably because the common site of extensive involvement of the aorta is in its ascending portion and is directed to the right. An interesting type of aortic disease that has recently attracted our attention because of the possibility of its confusion with coronary thrombosis, rather than with angina pectoris, is dissecting aneurysm of the aorta. Severe prolonged substernal pain, and usually upper back pain too, occur when the aortic wall is split, and sudden death may ensue hours or days later when the dissecting aneurysm ruptures into the pericardium or pleura.

Pericardial and pleural pain is easily differentiated from angina pectoris by its prolonged character, its usual aggravation by respiration, its association with an acute infection, and by the presence in most cases of a friction rub.

Finally, we come to four causes of pain in the upper chest not due to involvement of the cardiovascular apparatus itself. They are, first, trouble with the bones, joints, muscles, or bursae of the thoracic cage, spine, or arms due to muscle strain, arthritis, or bursitis. The differentiation of this type of pain from angina pectoris is simple in nearly every case because of its usual location in other than the substernal region, its aching character and prolonged duration, and its aggravation by certain movements or positions of the thorax or arms. The other three causes of chest pain simulating angina are all subdiaphragmatic in origin. They are peptic ulcer, gall-bladder disease, and gaseous distension of the gastrointestinal tract, particularly of the stomach and colon. The pain of peptic ulcer often radiates up under the sternum and may extend out to the left shoulder and

into the left arm or into both arms but it is burning rather than strangling in nature, it lasts more than a few minutes as a rule, and it is relieved by food. Gall-bladder pain rarely need be confused with angina pectoris, its maximal site is usually in the right upper quadrant of the abdomen or in the epigastrium, when it is referred to the chest it goes to the right shoulder or back in most cases, it is colicky in nature, often associated with vomiting, and it lasts for more than a few minutes. When it is of a character suggestive of heart pain it is coronary thrombosis rather than angina pectoris from which the gall-bladder disease must be differentiated. It must be recognized, however, that gall-stones and coronary disease not infrequently occur together in the same patient. The final condition, namely gaseous distension of stomach or colon, has for a long time been very confusing so far as the heart is concerned and has been in part responsible for the traditional misnomer of acute indigestion for angina pectoris and coronary thrombosis. However, this confusion should melt away in the light of our present knowledge and of careful study of individual cases. It is true that angina pectoris may be precipitated or its occurrence favored by distension of the stomach with food and air and by the increased metabolism that results from active digestion, it is also true that in some people constipation and distension of colon with gas and feces favor the occurrence of coronary pain, and finally it is true that relief of an individual attack of angina pectoris may or may not be attended by the belching of gas from the stomach, but these are all simply associated conditions, do not themselves give rise to typical substernal oppression which might be confused with angina pectoris, and are more likely to be absent than present. Their importance has been greatly exaggerated except as they may prove to be exciting or aggravating factors. Many people belch gas frequently and have persistent bloating of stomach and colon without angina pectoris and many people have angina pectoris without any gastrointestinal symptoms at all.

In leaving the differential diagnosis of angina pectoris I need simply add that there are a few other infrequent causes of chest pain easily distinguished from angina pectoris because of the character, duration, or site of the pain, such causes are herpes zoster, tabes dorsalis, mediastinal or bronchial tumors, and subdiaphragmatic hernias.

TREATMENT OF ANGINA PECTORIS

The *medical treatment* of angina pectoris is of great importance, contrary to the fatalistic belief of many doctors and laymen who are so impressed by the uncertainty of life in the cases of those afflicted that they consider it unnecessary to take any particular measures. Of immediate concern, of course, is the treatment of the attack itself and the traditional measures are well known to you all. rest and nitroglycerine or amyl nitrite. Standing or sitting stock still is of prime importance and alone may permit the attack quickly to subside. Recumbency is to be avoided; in fact when

the attacks come on at night in bed, the quickest relief is usually obtained by getting up at once and standing by the bedside. Some patients tell of their ability to walk off the attack, this is usually, I believe, impossible, and probably always dangerous. Inhalation of amyl nitrite from a pearl quickly dissipates the oppression through its vasodilating effect. Its strength, however, is rather overpowering for some people, it is sometimes a bother to break the pearl, and it is rather expensive for frequent use. Nitroglycerine in tablet form in the dosage of 1/200 grain crushed and dissolved in the mouth acts almost as quickly as does amyl nitrite, is more easily taken, and is less expensive. The larger doses of 1/100 and 1/50 of a grain of nitroglycerine should be used cautiously for not only may they give rise to unpleasant symptoms of excessive flushing of the face and throbbing and congestion in the head, but in sensitive individuals they may cause faintness, collapse, and actual syncope, as we have discovered in four of our own patients in the past two years. If no nitrites are available whisky and brandy may be used for relief of an attack but their action is rather slow. Morphine should not be resorted to except when the distress is maintained as with paroxysmal tachycardia or coronary thrombosis. A few patients have told me that certain exercises like deep breathing, contraction of the abdominal muscles, and belching of gas seem to help to abolish the substernal oppression of angina pectoris.

To prevent attacks of angina pectoris when this symptom has once appeared and to treat the underlying coronary disease, strict rules of rest and exercise and diet should be laid down. Medicinal therapy is far less important except under the following three circumstances: if luetic aortitis is present, careful but thorough antiluetic therapy should be instituted beginning with mercury or bismuth and potassium iodide and alternating such a course with one consisting of the administration of neoarsphenamine, if severe anemia is present it should be treated as indicated with liver extract or iron, if paroxysmal tachycardia occurs, quinidine sulfate rations may help. Vasodilating and sedative drugs given at intervals seem to help some individuals, especially the bromides or barbitol for nervousness, and they may be tried more or less routinely, often, however, they have no beneficial effect, and if so they need not be continued after a trial course. These drugs include theobromine, theophylline ethylene diamine, the nitrites, pancreatic and muscle extracts, carbon dioxide inhalations, barbitol compounds, and the bromides. There is one very useful procedure that may be adopted in rather severe cases, to help render life less miserable and more active, that is to use a nitrite like nitroglycerine prophylactically at intervals as needed to permit the accomplishment of necessary activity such as dressing in the morning, going to stool, and starting off to work. Such a measure should, however, be regarded as a privilege and not abused. It has proved helpful in a number of my patients and in some has been used advantageously instead of the alternative procedures of complete invalidism or of paravertebral alcohol injections. Similarly sodium nitrite or better still

erythrol tetranitrate may be given at night to help to prevent the angina of decubitus. The erythrol is sometimes too strong and causes headaches, if it does, the usual dose of $1/2$ grain may be reduced to $1/4$ grain. Finally, alcohol in the form of whisky or brandy may be used prophylactically at intervals, it is effective in some cases but it is probably not a good habit to establish and it is expensive. Digitalis has not proved of value in my cases, in fact in some it has apparently aggravated the trouble.

Of all therapeutic procedures for angina pectoris, rest is the most important and the most neglected. It is well to advise at the very beginning *saturation with rest* covering at least a few weeks or probably more beneficially a few months. Certainly angina pectoris is just as important as many other things like nervous prostration and tuberculosis that are treated by prolonged rest, and it is almost always benefited though usually not completely cured by such rest. Nature is striving to improve the coronary circulatory deficiency and the best way to help this natural tendency is to get rid of physical and nervous strain at least for the time being. Sometimes angina pectoris disappears altogether even without absolute rest but it is more likely to do so with rest. Nervous tension which is an important part of the background of angina pectoris is also benefited by rest and perhaps even more than is the coronary disease itself. Then after the initial saturation with rest, rations of rest periodically are invaluable, such rations may consist of weekends in bed regularly, a long weekend away from home every fortnight, a week of rest once a month, or a fortnight of rest every three months. There are various ways to work this out. Meanwhile there should also be a daily rest, for example, a lazy hour after luncheon, and bedtime should be early. To have breakfast in bed sometimes helps. For each case the doctor should prescribe the amount and time of rest and exercise as carefully as he would prescribe a medicine. But with all this, great care must be taken to avoid the establishment of a neurosis which may be more difficult to treat than the angina pectoris itself. A healthy optimistic attitude of mind must be constantly maintained by the doctor and inculcated in the patient, psychotherapy of this sort is invaluable.

Exercise within the patient's reserve is advisable. It is good to maintain proper tone of the general musculature of the body, to have the diaphragm in good working order, and to keep the brain and the bowels in condition by physical exercise, of which walking and mild calisthenics are the best for the cardiac patient. Golf is permissible if it is carried on in a leisurely manner and not on hilly courses, and if it does not cause angina pectoris. Fishing is often ideal. Most of the more strenuous games and sports are to be discountenanced. After every meal there should be at least one-half hour and preferably one hour of rest in the sitting position.

Excitement in contrast to exercise should be studiously avoided by patients with angina pectoris. It is unwise to take unnecessary risks, and to court excitement is such a risk. Contact with crowds may be included here. Anger is dangerous. Hurry and worry induce a nervous element that may be the last straw.

There are certain measures for the improvement of the general health that sometimes help also in reducing the frequency and severity of angina pectoris and even in rare cases in abolishing it altogether for the time being. Included in these measures, all of which are worthy of consideration, are the clearing up of focal infections like infected teeth, the correction of surgical conditions that give rise to distress or irritation such as gall-stones or hernias, the control of constipation, and the use of methods of physical therapy like carbon dioxide baths, massage, and perhaps diathermy. So far as I know these measures have only an indirect influence on angina pectoris, but if that influence is favorable it does not much matter whether it is direct or indirect. The regulation of habits and the institution of physical therapy under the pleasant and restful surroundings of some health resorts and spas are undoubtedly of benefit to some patients with angina pectoris, and periodic resort to such places once or twice a year for a few weeks may be well worth while. Caution should be exercised, however, against doing too much in the way of surgery, dentistry, or physical therapy in a short space of time.

Finally, we come to diet and climate. There is no special diet to be recommended in the treatment of angina pectoris, but there are simple rules. Hearty meals, food difficult to digest or noted as favoring the accumulation of gas, dinner at night, and stimulating drinks like strong coffee had best be avoided. As already advised there should be a rest period after meals. The use of alcoholic beverages need not be denied but heart symptoms will often follow any excess in this direction. Wine and beer perhaps are helpful in reducing the nervous tension in some people with angina pectoris. The low incidence of coronary disease in chronic alcoholism is, however, scarcely enough of a benefit to counterbalance the disagreeable character of the lives of such alcoholics and their cirrhotic livers. Most of my own angina pectoris patients have not used alcohol, of one group of 331 cases 194 or 59 per cent have been abstainers. However, one of the heaviest drinkers in my practice was one of those most seriously affected by angina pectoris in frequency and severity, the only possible benefits that he may have derived from his habit were that he lived a carefree life (he fortunately was able to) and that he survived 20 years of the angina pectoris.

Tobacco is probably a different matter. I am inclined to believe that it is wise to advise its omission in angina pectoris since it does in some individuals prepare the ground for attacks. Most patients claim that smoking makes little or no difference in influencing the frequency or severity of their angina pectoris. Of a series of 331 angina pectoris patients of my own 87 or 26 per cent smoked to excess, 100 or 30 per cent used tobacco moderately, and 144 or 44 per cent were non-smokers.

Little need be said about climate except that a mild climate winter and summer favors longevity in angina pectoris, it is important to avoid heat but much more important to avoid the cold.

Roentgen-ray treatment of angina pectoris has been proposed and tried

during the past few years, by radiation of the posterior nerve roots and the chain of sympathetic ganglia Little has come of it to date

For intractable angina pectoris in carefully selected cases paravertebral alcohol injections and nerve section have proved of value These methods of treatment are dealt with in the paper by Dr James C White

It has become my firm conviction, as the years of my experience with angina pectoris go by, that much may be done to make the lot of the victim of angina pectoris easier and happier, and to prolong his life Many of the catastrophes of sudden death in angina pectoris that we read about so often in the newspapers are avoidable; some are not We should do all we can to keep alive valuable members of society for the sake of their families, friends, and communities, and it is unfortunately just these valuable people who are apt to suffer from angina pectoris

Finally, in closing let me quote from an early English translation published in 1542 of the "Regiment of Helthe" of the University of Salerno, the medical school of note which flourished in Southern Italy in the Middle Ages Whether angina pectoris was one of the evil conditions to be prevented by following these rules we cannot say but it is likely that it was "The first doctrine is that he that desireth helth of body must eschew and avoyde great charges, thought, and care The second doctrine is to eschewe anger The thyrde doctryne is to eate and drynke sobrelly

The fourth doctrine is to make a light souper" The fifth doctrine advises exercise Some there be, however, who would prefer to follow Edna St Vincent Millay's poem where it is written

I burn my candle at both ends
It will not last the night
But ah my foes, and oh my friends,
It gives a lovely light

Between the extremes of complete disregard of health and excess of prudence there lies a middle course which should avoid presenile angina pectoris and yet allow one to enjoy a useful and a happy life

EXPERIMENTAL AND CLINICAL STUDIES IN THE SURGICAL TREATMENT OF ANGINA PECTORIS*

By JAMES C WHITE, M D , *Boston, Massachusetts*

FOLLOWING François-Franck's¹ suggestion that the pain of angina pectoris could be relieved surgically, Jonnesco,² Leriche,³ Danielopolu,⁴ and Hofer⁵ abroad, and Coffey and Brown⁶ in this country have developed operations for resecting part or all of the known cardiac nerves in the neck. These structures consist of the superior, middle, and inferior cervical sympathetic ganglia and their cardiac branches, also the depressor nerve when it is present as a separate branch of the vagus. All of these procedures have produced strikingly successful results in some cases, but none has been uniformly successful. As a result there has been complete confusion concerning the physiology of cardiac pain and its pathways to the central nervous system. This problem was bound to remain insoluble until an operative procedure could be devised which would give consistently successful results, or until a method could be found of studying cardiac pain in animals. Mandl's⁷ and Swetlow's⁸ method of paravertebral injection of the sympathetic ganglia is now promising to fulfill the first requisite, in that attacks of angina pectoris can be definitely stopped by successful injections of the upper thoracic sympathetic ganglia. The second requisite has been fulfilled by a recent discovery of Sutton and Lueth⁹ which has made possible the experimental production of cardiac pain in dogs.

Using this method, which consists of the temporary occlusion of the descending branch of the left coronary artery, White, Atkins, and Garrey¹⁰ have tested the efficiency of the different possible neurosurgical operations for denervating the heart in a series of 29 dogs.

In four control animals it was found that occluding the flow of blood in the descending branch of the left coronary artery for periods of from 15 to 30 seconds produced uniform and definite signs of discomfort in each dog.† It was impossible to maintain the occlusion for over 30 seconds without causing unnecessary suffering on the part of the animals. Division of both vagi or of the upper five pairs of intercostal nerves had no effect on the pain. (Table 1.) In seven dogs in which one or both stellate ganglia were removed evidences of pain were still present, as was also the case in two dogs after resection of the left sympathetic trunk from the stellate down through the fourth thoracic ganglion. But when this last named procedure was performed on both sides, no evidence of pain could be

* Read before the American College of Physicians at Montreal, February 10, 1933. From the Cardiac Clinic and the Surgical Services of the Massachusetts General Hospital.

† For want of a better word to describe the characteristic reaction to experimental coronary occlusion of this duration, the phenomena described above will be referred to hereafter as evidence of cardiac pain. But it is most important to emphasize that none of these animals was ever permitted to suffer acutely.

TABLE I

Efficiency of Various Neuro-Surgical Procedures in Interruption of Cardiac Pain Pathways in the Dog

	Dog	Neuro-Surgical Operation	Reaction to Occlusion of Coronary Artery
Controls	1	—	+++
	2	—	+++
	3	—	+++
	4	—	+++
	5	Stellate Ganglionectomy (Left)	+++
	5	" " through D ₄ (Left)	+
	7	" " D ₅ (Left)	+++
	8	Bilateral Stellate Ganglionectomy	++
	9	" " "	++
	10	" " "	++
	11	" " "	+
	12	" " "	++
	13	" " "	++
	14	" " " through D ₄	0
	15	Posterior Root Section, D ₃ -D ₇ (Left)	+++
	16	" " " D ₁ -D ₄ (Left)	+
	17	" " " D ₁ -D ₄ (Right & Left)	+++
	18	Anterior and Posterior Root Section, D ₁ -D ₅ (Right & Left)	0
	19	Posterior Root Section, D ₁ -D ₅ (Right & Left)	0
	20	Intercostal Nerves, D ₁ -D ₅ (Right & Left)	+++
	21	Division of Vagi (Right & Left)	+++

elicited Two dogs in which the upper five posterior spinal roots were cut bilaterally also showed no evidence of pain Protocols and kymographic tracings of these experiments are given in the recent paper referred to above¹⁰

From these experiments it is apparent that only removal of the upper thoracic ganglia or section of the corresponding posterior spinal roots can cut all the afferent connections between the heart and the central nervous system There must therefore be direct connections between the second, third, fourth, and possibly the fifth thoracic ganglia and the heart which cannot be reached by any of the classical operations in the neck

Observation of the motor response of the heart to stimulation also shows direct connections between the thoracic ganglia below the stellate and the heart While faradic stimulation of the stellate ganglia causes an increase of heart rate up to 80 per cent, stimulation of the second and third thoracic ganglia after resection of the stellates causes an acceleration of heart rate up to 58 per cent (Table 2) In some instances there was an even greater increase in pulse rate on stimulating the second and third thoracic ganglia than on stimulation of the stellates These observations corroborate the work of Cannon, Lewis, and Britton¹¹

Previous operators have felt that removal of the cervical sympathetic ganglia with their superior, middle and inferior cardiac nerves was sufficient to denervate the heart This was a natural supposition, as no other sympathetic cardiac nerves were known five years ago That 40 per cent

TABLE II

Increase in Heart Rate on Sympathetic Trunk Stimulation

Dog	Stellate	D ₁ & D ₂
22	11% Left	—
23	78% Right	—
24	80% Right	—
25	75% Right	—
26	88% Right	7% Left
27	20% Left	55% Left
28	10% Right	28% Left
29	4% Left	58% Right

Faradic stimulation of stellate or of 2nd and 3rd thoracic ganglia after section of the vag or their paralysis with atropine. The figures recorded above represent the greatest percentage increases in heart rate which were obtained. In Dog 25, the spinal cord had been previously transected in its third cervical segment and both adrenal glands had been removed, in order to eliminate the possibility of any reflex stimulation of the brain centers or the adrenal glands.

of these operations were failures is probably accounted for on the basis that surgeons neglected these direct thoracic connections which we have described running between the heart and the sympathetic ganglia below the level of the stellates (Figure 1). These connections have recently been shown in the anatomical dissections of Jonnesco and Enarchesco,¹² Braeucker,¹³ and Kuntz and Morehouse.¹⁴ Their physiological importance in conducting both afferent and efferent impulses is shown in our experiments.

Clinical results based on these anatomical and physiological findings are as follows. Where the sympathetic ramus and ganglia were blocked with alcohol in 28 cases of severe angina pectoris, 57.6 per cent of cases were entirely relieved of their attacks on the injected side, another 23.1 per cent were greatly benefited, 7.7 per cent were but slightly improved, and only 11.6 per cent were failures. All of these cases were carefully selected by Dr. Paul Dudley White as being the most severe or obstinate cases of angina pectoris coming to the clinic. Milder cases which could be maintained in even relative comfort on a medical regime were never treated surgically. None was refused on account of being too sick, although several would have been impossible risks for any form of nerve resection. All were totally unable to perform any kind of work, and several were having many attacks while at rest in bed. Many had had previous coronary thrombosis. In spite of this, good results were achieved in 80 per cent of the cases treated by alcohol injection, as against 58 per cent reported for the several varieties of cervical sympathectomy.* Each case of failure appears to have been due to faulty injection. Outside of one death from bronchopneumonia in a moribund woman of 85, no serious complications have resulted from these injections, but a varying degree of alcoholic neuritis of the intercostal nerves is a frequent and at times a most annoying complaint after injection therapy.

In four cases where the sympathetic ganglia have been resected from the

* Three further patients with aneurysm of the aortic arch were entirely relieved of their pain by injection of only the first and second thoracic ganglia.¹⁵

For the technique of performing paravertebral alcohol injection, see previous papers by the writer.^{16, 17, 18}

first through the fourth thoracic segments, relief has been complete in three. The fourth continues to have mild attacks in the arm area, presumably transmitted through the upper portion of the stellate ganglion, which was not excised. Of even greater significance in favor of the correctness of this theory of the anatomical pathways of cardiac pain, is the fact that two of these cases who died subsequently of coronary occlusion had intense right-sided pain in the attack, without any discomfort on the operated left side.

Since the completion of our animal investigations, we have not had a suitable case for posterior root section, but of three cases where this operation has been utilized by Davis¹⁹ and by Cone²⁰ since this work has been completed, all have been relieved.

Table 3 shows in summarized form the type of case, the method of treatment, and the result obtained in our series of 32 injections or operations for angina pectoris.

We believe that these findings point to a rational conception of the cardiac pain pathways and that their application should promise more satisfactory results in the surgical treatment of angina pectoris. It is our personal opinion that the effectiveness of these procedures is due to blocking the afferent pain pathways from the heart. We are aware, however, that this point has not been fully proved and that some writers believe that the benefit of operation is due to interrupting cardio-pressor reflexes. Our experimental findings demonstrate that it is equally important in either event, to use a thoracic, rather than a cervical approach. Paravertebral alcohol injection is the safest method at our disposal, but fails to give satisfactory relief in a fifth of the cases because of its technical difficulty. Resection of the upper thoracic ganglia or section of the corresponding posterior spinal roots appears to offer nearly certain relief, but the mortality from these radical procedures is certain to be appreciable. On this account we plan to employ alcohol injection on patients with angina pectoris who fail to obtain sufficient relief from medical measures. In the small percentage of cases which fail to obtain adequate relief, the resulting fibrosis of the parietal pleura will make ganglionectomy a difficult procedure, but it will in no way interfere with the subsequent exposure and sectioning of the posterior roots in suitable cases.

SUMMARY

1 Pain from the heart and the ascending arch of the aorta is conveyed to the sympathetic trunk by fibers running in (a) the middle and inferior cardiac nerves to the corresponding cervical sympathetic ganglia, (b) recently discovered nerves which run directly across the mediastinum from the posterior cardiac plexus to the upper thoracic sympathetic ganglia.

The painful stimuli thence enter the spinal nerves through the white communicant rami. As there are no white rami in the cervical region, all

TABLE III
Patients Treated Surgically for Angina Pectoris at the Massachusetts General Hospital, 1927-1933

Patients Treated by Paravertebral Alcohol Injections						
No.	Age	Diagnosis	Treatment	Relief	Duration	Status at Last Report
1	54	Syphilitic aortitis, aortic regurgitation, hypertension, angina pectoris, confined to bed, angina decubitus, 15 attacks daily. Much milder attacks on right	D ₁ -D ₃ Left 2/27 D ₃ -D ₇ Right 3/28	100% 0	6 yrs	Unable to work, but fairly comfortable. Partial decompensation. Patient is in better condition today than before his first injection
2	60	Hypertensive and arteriosclerotic heart disease, aortic regurgitation, angina pectoris, previous attack of coronary occlusion, slight congestive failure	D ₇ -D ₈ Left 5/27 Re-injection D ₁ -D ₃ 6/27	60%	To death, 7 mos	Able to resume light work until sudden death undoubtedly from coronary thrombosis or angina pectoris, on Feb 8, 1928, no autopsy
3	53	Arteriosclerotic heart disease, hypertension, angina pectoris at rest	D ₁ -D ₈ Left 6/27	25%	To death, 2½ yrs	Up and about, quietly active, appearing good health but with moderate angina pectoris. Died of empyema
4	51	Moderate arteriosclerosis and enlarged heart, angina pectoris, incapacitated	D ₁ -D ₈ Left 7/27	100%	To last report, 2½ yrs	In fair health, but still has right-sided angina pectoris (mild), resumed work as truck-driver for 3 months, but is too short of breath now
5	56	Arteriosclerotic heart disease, hypertension, myocardial insufficiency, previous coronary thrombosis	D ₁ -D ₈ Left 8/27	40%	To death, 4 mos.	Died suddenly on Jan 9, 1928, undoubtedly of coronary thrombosis or angina pectoris, no autopsy
6	52	Hypertensive heart disease, aortic regurgitation, angina pectoris at rest	D ₁ -D ₈ Left 11/27	100%	To last report, 2½ yrs	Comfortable and able to do light work, 5 mos
7	58	Arteriosclerotic heart disease, hypertension, angina pectoris	D ₁ -D ₈ Right 3/28	65%	To last report, 5 mos	Fairly comfortable and has resumed light work
8	68	Arteriosclerotic heart disease, hypertension, angina pectoris, previous coronary thrombosis	D ₁ -D ₈ Left 4/28	50%	To death, 10 mos	Comfortable, mild angina pectoris daily, but able to be quietly up and about. Died of coronary thrombosis

TABLE III—Continued

No	Age	Diagnosis	Treatment	Relief	Duration	Status at Last Report
9	47	Hypertension, arteriosclerosis, coronary thrombosis, angina pectoris, confined to bed	D ₁ -D ₈ Left 9/28	100%	To death, 2 mos	Died of myocardial failure with right-sided angina pectoris on Nov 4, 1928
10	51	Arteriosclerotic heart disease, coronary thrombosis, angina pectoris, morphinism	D ₁ -D ₈ Left 9/28	—	No pain to death, 3 weeks	Five days later another attack of coronary thrombosis, died Oct 4, died too soon to judge
11	56	Hypertensive and arteriosclerotic heart disease Angina on exertion	D ₁ -D ₈ Left 6/29	100% 50%	4 mos To death, 22 mos	Worked for 4 mos, then a stroke arms after that
12	57	Hypertensive and arteriosclerotic heart disease Angina on exertion	D ₁ -D ₄ Left 10/29	90% 50%	4 mos 3½ yrs	Still able to do light work
13	56	Arteriosclerotic heart disease, coronary thrombosis Angina on exertion	D ₁ -D ₄ Left 10/29	100% 60%	1 yr 3½ yrs	Still practising medicine
14	54	Arteriosclerotic heart disease, coronary thrombosis, decompensation, angina decubitus	D ₁ -D ₄ Left 10/29	100%	?	Followed only 2 weeks
15	49	Arteriosclerotic heart disease, angina on any exertion	D ₁ -D ₈ Left 10/29	90% 50%	3 mos 17 mos	Returned to work
16	57	Arteriosclerotic heart disease, angina on exertion	D ₁ -D ₄ Left 11/29	0		Continues as before treatment
17	52	Syphilitic heart disease, aortitis, angina decubitus	D ₁ -D ₄ Left 11/29	0		Continues as before treatment
18	70	Arteriosclerotic heart disease, aortic stenosis, hypertension, angina pectoris	D ₁ -D ₈ Left 11/29	100%	To last report, 26 mos	Continues pain free and can climb two flights of stairs without oppression

TABLE III—Continued

No.	Age	Diagnosis	Treatment	Relief	Duration	Status at Last Report
19	64	Arterio-sclerotic heart disease, coronary occlusion, angina pectoris for 8 years, attacks increasing, come on slightest exertion	D ₁ -D ₄ Right 3/30	100%	To last report, 27 mos	Doing light housework
20	63	Arterio-sclerosis, hypertensive heart disease, aortic regurgitation, angina pectoris	D ₁ -D ₃ Left 4/30	50%	To last report, 8 mos	Returned to work as lawyer
21	63	Mitral stenosis with severe pain in precordium and partial decompensation	D ₁ -D ₆ Left 1/31	100%	To death, 10 mos	Unable to work because of dyspnea Died during operation on mitral valve at another hospital
22	59	Hypertensive heart disease, angina pectoris	D ₁ -D ₄ Left 2/31	75%	To last report, 24 mos	Reports mild pain in left arm, none in chest
23	53	Rheumatic heart disease, coronary occlusion, angina pectoris	D ₁ -D ₄ Left 9/31 D ₂ -D ₆ Left 10/31	Pain in arm stopped 100%	To death, 4 mos	Died of decompensation and without recurrence of angina pectoris
24	61	Arterio-sclerotic heart disease, coronary occlusion, angina pectoris	D ₁ -D ₄ Left 9/31	90%	15 mos	Unable to work on account of dyspnea
25	55	Arterio-sclerotic heart disease, angina pectoris, advanced cerebral arteriosclerosis Patient exhausted by severity and frequency of attacks Injection performed with realization that patient was moribund	D ₁ -D ₂ Right 10/31	Apparently complete		Died of bronchopneumonia 2 days later
26	61	Arterio-sclerotic heart disease, moderate hypertension, coronary occlusion, angina pectoris	D ₁ -D ₄ Left 12/31	60%	1 yr	Very mild attacks after injection Died of cardiac failure without pain
27	60	Arterio-sclerotic heart disease, hypertension, angina pectoris	D ₁ -D ₃ Left 9/32	—	4 mos	Insufficient ganglia injected with only slight relief Should have D ₄ and D ₅ injected

TABLE III—Continued

No	Age	Diagnosis	Treatment	Relief	Duration	Status at Last Report
28	54	Arteriosclerotic heart disease and coronary occlusion Constant precordial pain with frequent severe attacks of angina pectoris Patient exhausted with suffering	D ₁ -D ₃ Left 1/33	100%	—	Only 3 weeks have elapsed since injection, but the relief of his constant pain and of the dread of his severe attacks, together with the resultant ability to sleep and eat, have produced a dramatic transformation He appears to have gained a new lease on life
4 Cases Treated by Thoracic Ganglionectomy						
29	20	Rheumatic heart disease and aortic regurgitation Angina pectoris up to 15 times a day Severe precordial pain on left, mild on right	D ₁ -D ₃ Left 2/5/29	100%	To death	Mild right-sided attacks constituted a good warning signal Died of cardiac decompensation and coronary occlusion 8 months later Attack of agonizing pain in right precordium lasted 3 hours before death No pain on left
30	29	Syphilitic aortitis with closure of mouths of coronary arteries Angina pectoris	D ₁ -D ₃ Left 9/19/29	100%	To death	Excellent postoperative convalescence On 13th day developed symptoms of coronary occlusion Died after 4 hours of terrific pain in right precordium, none on left side Autopsy coronary occlusion
31	60	Arteriosclerotic heart disease and angina pectoris	D ₁ -D ₃ Left 10/1/29	90%	To date	Mild anginal attacks on unoperated right side She still has some radiation to left arm, but gets along comfortably on medical measures which did not give her sufficient relief before operation
32	62	Arteriosclerotic heart disease with coronary thrombosis leading to angina pectoris	D ₁ -D ₃ Left 10/1/29	100%	To death	This patient had no money, felt he had to work, and demanded being subjected to operation with knowledge of its greater risk in order to be sure of relief He developed postoperative pneumonia, but was discharged in 3 weeks No further pain One month later died painlessly of coronary thrombosis Autopsy showed occlusion of both coronary arteries

Note The percentage of relief was estimated at follow-up examinations in the Cardiac Clinic by Dr Paul D White These figures apply only to the side injected or operated upon, as the unoperated side was never affected The duration of improvement is dated to last report
Six of the alcohol injections summarized above were done by Dr W J Mixer, the remaining ones by Dr J C White
The thoracic ganglionectomies were performed by Drs W J Mixer, A W Allen, and J C White

pain sensation referred over the cervical sympathetic trunk must descend to the upper thoracic ganglia before it can reach the spinal cord. Therefore impulses traversing either of these routes converge on the upper thoracic sympathetic ganglia to reach the spinal cord via their white rami communicantes and the corresponding posterior spinal roots.

Pain referred to the left or right precordium or the arm enters the cord only on the same side.

The vagus nerve carries no important pain fibers from the heart.

Desensitizing the skin areas to which cardiac pain is referred by section of intercostal nerves does not give permanent relief of cardiac pain.

2 Operations on the cervical sympathetic trunk, even if they include the stellate ganglia, cannot interrupt all the pathways of cardiac pain.

3 The upper thoracic sympathetic ganglia or their communicant rami or the posterior roots of the corresponding spinal nerves are the logical points at which to interrupt painful stimuli from the heart.

4 These anatomical and physiological premises have been put to the test in 32 cases. In each case where we have been sure of a successful interruption of the above mentioned structures, angina pectoris has disappeared.

5 Paravertebral alcohol injection is difficult technically because of the depth of the nerves and the small areas sclerosed by the alcohol. However, it is the safest method that we have and its results are far better than the old forms of cervical sympathectomy.

6 The upper thoracic sympathetic ganglia have been resected in four cases, with striking relief of pain on the operated side. We believe, however, that this is too severe an operation for the average patient suffering from angina pectoris.

7 We believe that the best surgical procedure consists of first attempting to block the thoracic sympathetic nerves with alcohol. The cases which fail to obtain satisfactory relief, provided they are reasonably good surgical risks, can finally be subjected to section of the posterior spinal roots.

BIBLIOGRAPHY

- 1 FRANCOIS-FRANCK M. Signification physiologique de la resection du sympathique, Bull Acad de Méd Paris 1899, xli 565
- 2 JONASCO, T. Traitement chirurgical de l'angine de poitrine par la résection du sympathique cervico-thoracique Bull Acad de Méd, Paris 1920, lxxxiv 93
- 3 LEECH, R. and STRICKER, R. The surgical treatment of angina pectoris, Heart, 1928, iii 649
- 4 DANIELOVIC, D. L'angine de poitrine et l'angine abdominale 1927, Masson, Paris
- 5 HORST, G. Zur Chirurgie des vegetativen Nervensystems bei Angina Pectoris, Wien Med Wochenschr Nos 31 and 44, 1925
- 6 COATES, W. B. and BEAVER, P. K. The surgical treatment of angina pectoris, Arch Int Med, 1923 xxxi 200
- 7 MAYER, F. Die Wirkung der paravertebralen Injektion bei Angina Pectoris, Arch f Klin Chir 1925 cxvxi 405
- 8 S. WHITE, G. Paravertebral block in cardiac pain. Am Heart Jr, 1926, i, 1

- 9 SUTTON, D C, and LUETH, H C Pain, Arch Int Med, 1930, xlv, 827
- 10 WHITE, J C ATKINS, J A, and GARREY, W E Experimental and clinical studies on the surgical management of angina pectoris, Arch Surg, 1933, xxi, 765
- 11 CANNON, W B, LEWIS, J T, and BRITTON, B W A lasting preparation of the denervated heart for detecting internal secretion with evidence for accessory accelerator fibers from the thoracic sympathetic chain, Am Jr Physiol, 1927, lxxvii, 326
- 12 JONNESCO, D, and FNARCHESCO, M Nerfs cardiaques naissant de la chaine thoracique du sympathique au dessous du ganglion stellaire, Compt rend Soc de biol, 1927, xcvi, 977
- 13 BRAFUCKER W Der Brustteil des vegetativen Nervensystems und seine klinische chirurgische Bedeutung, Beit z Klin d Tuberc, 1927, lxxvi, 1
- 14 KUNTZ A, and MOREHOUSE, A Thoracic sympathetic cardiac nerves in man, Arch Surg, 1930, xx, 609
- 15 WHITE, J C Painful aneurysms of the aortic arch, J Am Med Assoc, 1932, xcix, 10
- 16 WHITE J C, and WHITE, P D Angina pectoris, treatment with paravertebral alcohol injections, Jr Am Med Assoc, 1928, xc, 1099
- 17 WHITE, J C Angina pectoris, relief of pain by paravertebral alcohol block of the upper dorsal sympathetic rami, Arch Neur and Psych, 1929, xxi, 302
- 18 WHITE, J C Angina pectoris, treatment by paravertebral alcohol injection or operation based on the newer concepts of cardiac innervation, Am Jr Surg, 1930, i, 98
- 19 DAVIS, L Personal communication
- 20 CONE, W V Personal communication

MANAGEMENT OF EDEMA *

By CHARLES A ELLIOTT, M D , F A C P , *Chicago, Illinois*

THE DISCOVERY that certain forms of edema are readily influenced by diet and by other therapeutic measures is one of the important contributions to clinical medicine of the past decade

A certain small amount of fluid normally exists in the intercellular spaces of the body. When it accumulates in quantity it is called edema. Edema may be local or general, hidden or grossly manifest. Fluid may accumulate in the serous cavities as a part of the general process with no essential difference in mechanism. Edema may occur in clinical conditions that are apparently quite dissimilar—in inflammation, allergic states, anemia, malnutrition, nephritis and cardiac failure. The mode of production probably varies greatly with each type. Undoubtedly many factors are involved. Of these, increased hydrostatic pressure and consequent increased capillary permeability, disturbances of osmotic pressure, and variations in the acid-base balance of the serum and tissues are best known and lend themselves most readily to therapeutic manipulation.

It is interesting to note that Richard Bright, in his writings which appeared in the *Guy's Hospital Reports* from 1827 to 1843, recognized that the albuminuria of nephritis occurred at the expense of serum protein, and implied that dropsy was aggravated by blood letting—then a common therapeutic procedure—due to the depletion of blood proteins. In 1903 Widal in France and Strauss in Germany observed the marked effect that the administration or withdrawal of salt in the diet had upon edema. Widal's classical case in which he was able to increase or reduce edema at will by the administration or withdrawal of salt is well known. These observations appear to be the beginning of the modern clinical study of edema. It is to be regretted that the significance of the observations of these clinicians remained so long unappreciated.

The clinical and experimental study of the mechanism and management of edema has been tremendously accelerated in recent years. At the present time various phases of the problem are being studied in many clinics. Undoubtedly with the development of new concepts concerning the mechanism of edema the details of management will change greatly during the next few years. However, from the great mass of recent experimental studies many observations of practical therapeutic value have emerged, concerning which there can be no reasonable doubt. In formulating practical procedures for the control of edema advantage should be taken of such established facts. A few only may be mentioned at this time. An excellent

* Presented to the American College of Physicians, Montreal, Canada, February 9, 1933.
From the Medical Department, Northwestern University Medical School and Passavant
Hospital, Chicago.

review of the subject with an extensive bibliography has recently been published by Peters¹

1 *The state of the kidneys*, save under exceptional conditions, has little to do with the mechanism which determines the retention of fluid in the body. In acute nephritis a hyperemic plethora with retention both of salt and water may occur, conceivably solely the result of kidney damage. In chronic and subacute diseases the functional reserve of the kidneys, however, is so great that sufficient renal function is usually preserved to carry on adequate renal work even in the presence of gross kidney damage.

2 *The restriction of water intake*, save under unusual conditions, does not materially contribute to the relief of edema. In fact, edema may increase or decrease independently of the water intake. While the ingestion of inordinate amounts of water may induce edema, water taken in ordinary amounts serves as an excellent diuretic. The radical restriction of fluid intake, therefore, is not included in the ideal diuretic regimen.

3 *In the presence of failing circulation* with increased hydrostatic and filtration pressure, edema appears to be due not only to mechanical interference in circulation but also, in part at least, to interference with peripheral cellular physiologic processes such as the $O-CO_2$ exchange. Therefore, therapeutic measures directed toward improvement of the circulatory status, such as bed rest, cardiac stimulants (digitalis and strophanthus) and oxygen therapy constitute an important part of the regimen directed toward the relief of edema of this type.

4. *The serum proteins* appear of first importance in maintaining the osmotic equilibrium as between the cellular elements and fluids of the body. The importance of maintaining a normal serum protein level in the face of disease is, I believe, not sufficiently realized. The physiologic integrity of the tissues is largely dependent upon the availability at all times of an adequate supply of serum proteins. The normal level of 5 or 6 grams per cent is readily maintained under normal conditions by a daily ration containing one gram protein per kilo of body weight. Depletion of serum protein occurs clinically as a result of protein restriction in diet, protein waste as in albuminuria, or as a result of disturbed metabolic processes. Since it is well established that the concentration of the electrolytes of the serum varies inversely with the concentration of the proteins, depletion of serum protein automatically raises the concentration of the total base. When serum proteins are depleted below a level of 3 or 4 grams per cent, edema may appear as a compensatory process, hydration of the body and a great increase in the salt content of the serum result, as reported by Leiter,² Barker and Kirk,³ and Shelburne and Egloff.⁴ Disturbances of the protein content of the serum may, therefore, determine the state of hydration of the body. Efforts to maintain an adequate protein concentration in the serum should include the prescription of a diet containing sufficient protein to cover inordinate consumption of protein in metabolic diseases such as hyperthyroidism and diabetes, and loss by way of the kidneys as in albuminuria. Save in the

presence of nitrogen retention this may be accomplished without difficulty. Blood transfusions or the intravenous injection of acacia as recently recommended by Hartmann, Senn, Nelson and Perley,⁵ may serve as temporary substitutes.

5 *Disturbances of the acid-base equilibrium* of the serum are probably of *second* importance in determining the state of hydration of the body, they lend themselves readily to therapeutic manipulation.

In this connection it should be remembered that *sodium* makes up more than 90 per cent of the total base of the blood serum and extracellular fluids, that potassium, calcium and the other bases, essential as they are for normal growth and cellular physiologic processes, are, from the point of view of the acid-base balance, of negligible importance since they represent not more than 10 per cent of the total base of the extra-cellular fluid. Therefore, as far as practical therapeutic procedures are concerned, what is said of total base applies almost equally well for sodium in the form of salt. Salt and water within the body appear almost inseparable. It is difficult, if not impossible, to retain salt without water or water without salt, about six grams of salt will hold about one liter of water. Since about one-third of the total base is balanced by protein or other colloids, given a low serum protein the amount of edema is determined almost if not quite accurately by the amount of salt administered in the diet. Since the greater part of the three to six grams of sodium in the daily diet is added to food as seasoning in the form of salt, it is a relatively easy matter to control the total base by withholding salt. The two to four grams of *potassium* in the daily diet are naturally present in animal and vegetable tissues consumed as food. The alleged antagonism between sodium and potassium may, in part at least, be ascribed to the characteristic distribution of these elements within the tissues, potassium being predominantly within the cells, whereas sodium predominates in the intercellular fluids. It is possible that the bulk of the potassium which occurs in the serum is that which is in transit to or from the cells. The diuretic action of potassium has long been known and applied in practical therapeutics. The mechanism by which it occurs is not clear. It has been suggested that it acts as a substitution product for sodium, this, however, seems unlikely. Whether potassium in the serum in concentrations encountered in clinical practice may be toxic is a debatable question. Toxic manifestations ascribed to potassium may be due to sodium loss. *Chloride* apparently acts solely as a vehicle for the metals, and edema is not ascribed to the inability of the kidneys to excrete chloride, hence the total chloride of the diet is probably of little practical significance.

The mechanism by which readjustment of the acid-base balance of the extracellular fluids of the body occurs may be briefly stated as follows. The body as a whole may be considered as a physio-chemical system in which acid and base are held in equilibrium as neutral salts. The equilibrium is delicately maintained. The alteration of one factor automatically alters all others. The total base concentration is the major, immediate factor which

controls the state of hydration. In other words, base holds water. Finally, procedures which tend to shift the reaction of the tissues and extra-cellular fluids toward the acid side—that is, withholding base or administering acid—result in the excretion of base and with it water. Practically this is quite readily accomplished by a low salt diet and the administration of an acid-liberating substance such as ammonium chloride, ammonium nitrate, calcium chloride, or hydrochloric acid in sufficient quantity, or by prescribing a diet that leaves a definitely acid ash. Some of the processes involved in this seemingly simple reaction are still obscure.

The considerations mentioned should be kept in mind in prescribing a practical diuretic regimen for the individual patient. Of first importance is the selection of a diet which will meet the nutritional requirements of a patient who is chronically ill. Otherwise much harm may be done. The diet must be balanced with respect to carbohydrate, protein and vitamin content, it must be adequate in amount and palatable, and for the purpose must facilitate the mobilization and elimination of fluid. Ideally, foods should be selected which leave a neutral or acid ash and which have a low sodium and high potassium content. This may readily be accomplished by reference to reliable tables showing the ash constituents of foods, such as those published by Sherman.⁶ Salt should not be used in the preparation of food, nor should it be used as a condiment, potassium chloride, however, may be added from a shaker as a fairly satisfactory substitute. Theoretically and practically, as reported by Barker,⁷ it is possible to eliminate edema in many cases solely by the dietary measures described. The addition of potassium chloride sprinkled on food as condiment or "salt substitute" may materially increase the potassium-sodium ratio and facilitate diuresis. In some patients the simple procedure of withholding sodium chloride in the preparation of food or its use as a condiment, and the administration of an acid-liberating salt such as ammonium nitrate in sufficient quantity to overbalance the sodium intake, may effect diuresis and eliminate edema. The administration of an acid-liberating salt of this nature appears, therefore, to be a matter of convenience where great care in the selection of a diet and its preparation may be difficult. Ammonium nitrate in 25 per cent solution in a simple vehicle is well tolerated and may be given in doses up to nine grams daily without serious inconvenience to the patient. Theoretically the acid radical split off from ammonium nitrate should have a diuretic effect on its own account.

The results obtained may on occasion be greatly enhanced by inducing an acute diuresis by means of mercurial or other diuretic preparations. In recent years *salyrgan*, an organic mercurial preparation containing 36 per cent mercury, has come into general use. One or two cubic centimeters of this solution introduced intravenously or deep into the muscles may be effective. It would appear from the reports of Christian and Bartram⁸ and of Hermann, Stone and Schwab⁹ that mercury has a general specific effect on the colloids of the body as well as a local effect upon the tubular epi-

thelium of the kidney, depressing tubular reabsorption of the electrolytes and water of the glomerular filtrate. The exact mechanism by which this is accomplished seems obscure.

The principles enumerated have a wide application in clinical medicine, the elimination of edema as seen in cardiac failure and nephritis, the reduction of the heart load, the relief of hypostasis, and the removal of pleural and ascitic fluids may prove of material benefit to many patients suffering from a wide variety of diseases. These means may be readily used in general practice over long periods of time both in ambulatory and bed-fast patients. The dangers incident to this method of management are relatively few, however, one does not contemplate the manipulation of forces which may dislocate or readjust the internal environment without giving the possibilities of doing harm serious thought. Practically no serious harm by such management has been recognized. Acidosis in its milder grades has been produced but is readily recognized and as easily combatted. Dehydration of severe grade should be avoided, but this too may be anticipated and prevented by modifying the regimen, by allowing a small amount of salt to be used in the preparation of food, or by reducing the dose of acid-forming salt if such has been prescribed. Methemoglobinemia may be produced in some by administering ammonium nitrate in the doses usually prescribed but it is readily recognized and as readily relieved, as reported by Barker and O'Hare,¹⁰ Eusterman and Keith,¹¹ and Tarr.¹² Finally, patients themselves, by closely observing their general condition, especially as to body weight or the re-appearance of ankle edema, may soon learn to adjust their own diuretic regimen satisfactorily.

REFERENCES

- 1 PETERS, J. P. Salt and water metabolism in nephritis, *Medicine*, 1932, **xi**, 435-535
- 2 LEITER, L. Experimental edema, *Proc Soc Exper Biol and Med*, 1928, **xxvi**, 173
- 3 BARKER, M. H., and KIRK, E. J. Experimental edema (nephrosis) in dogs in relation to edema of renal origin in patients, *Arch Int Med*, 1930, **xlv**, 319-346
- 4 SHILLBURN, S. A., and EGLOFF, W. C. Experimental edema, *Arch Int Med*, 1931, **xlvi**, 51-69
- 5 HARTMANN, A. F., SPAN, M. J. E., NELSON, M. V., and PERLEY, A. M. The use of acacia in the treatment of edema, *Jr Am Med Assoc*, 1933, **c**, 251-254
- 6 SHILMAN, H. C. *Chemistry of food and nutrition*, Fourth Edition, 1932, Macmillan Co., New York
- 7 BARKER, M. H. Edema as influenced by a low ratio of sodium to potassium intake, clinical observations, *Jr Am Med Assoc*, 1932, **xcviii**, 2193-2197
- 8 CHRISTIAN, H. A., and BARTMAN, E. A. Experimental observations of the action of diuretics, *Trans Assoc Am Phys*, 1932, **xlvi**, 293
- 9 HEIMANN, G., STONE, C. T., and SCHWAN, E. H. Some studies on the mechanism of diuresis in patients with congestive heart failure, *Trans Assoc Am Phys*, 1932, **xlvi**, 279
- 10 BARKER, M. H., and O'HARE, J. P. The use of salyrgan in edema, *Jr Am Med Assoc*, 1928, **xix**, 299-304
- 11 EUSTERMANN, G. B., and KEITH, N. M. Transient methemoglobinemia following administration of ammonium nitrate, *Med Clin N Am*, 1929, **xii**, 1489-1496
- 12 TARR, L. Transient methemoglobinemia due to ammonium nitrate, *Arch Int Med*, 1923, **l**, 32

PROBLEMS OF PULMONARY TUBERCULOSIS IN GENERAL PRACTICE*

By RICHARD FITZ, M D , *Boston, Massachusetts*

FOR SEVERAL years I have been physician to the students at the Harvard Medical School. This experience has led inevitably to a deep interest in the clinical manifestations of pulmonary tuberculosis. I have been dismayed at the seriousness of this disease as it is found in a general practice of this sort. I have been struck by its varied appearance and, above all, I have been impressed by the great responsibility resting upon the family doctor in regard to it. Upon him much depends regarding the early diagnosis of tuberculosis, and his advice on the problems arising in the regulation of such patients' lives is often of paramount importance.

The tuberculosis problem has reached a queer impasse. This disease should be of widespread significance to all doctors, for in 1931, 80,562 new patients were admitted to the 509 special tuberculosis hospitals in the United States. And yet the Commission on Medical Education, in studying the diagnoses reported by a group of general practitioners, finds that the diagnosis of tuberculosis is an uncommon one. The reason for this discrepancy between the frequency of tuberculosis in the community and the rarity of its recognition by the general practitioner is not difficult to explain. Anti-tuberculosis propaganda and the development of specialists in tuberculosis have produced an apathy on the part of many doctors toward this disease. The family doctor thinks that he no longer sees the cases as he used to only at infrequent intervals do they pass through his hands, for now they are apt to be recognized and segregated by school physicians, industrial physicians, life insurance examiners, or by some special agency designed to combat the spread of the disease. Most cases, too, are treated while the disease is active by specialists in special hospitals. The result is that the general practitioner has lost interest in this subject. He has grown careless in the art of history-taking and physical diagnosis, and has washed his hands of the treatment of tuberculosis. This is an unfortunate state of affairs, for the general practitioner, in spite of the trend of the times, should be as keenly alive to the clinical problems of tuberculosis as ever. If he is a good doctor, his patients and their families will always eventually return to him for advice, no matter through what special hands they may pass on the way, and he remains their court of last appeal. If he is to give sound advice in regard to tuberculosis he must be familiar with it.

There are four clinical types of pulmonary tuberculosis in young people which have aroused my particular interest. These are familiar to every one and easily recognized. The individual cases which I shall present however, will serve to illustrate some of the reasons why the problems of

* Read before the American College of Physicians, Montreal, February 8 1933

pulmonary tuberculosis continue to be of vital importance to the family doctor

A young woman, 20 years old, came to the Peter Bent Brigham Hospital in October 1923. Early in the previous spring she had felt unusually tired and lacked her customary buoyancy. Gradually she began to lose a little weight, and presently it was observed that she had a slight afternoon temperature. She went to see two doctors before she came to the Hospital. One said that she was nervous, the other that he could find nothing wrong beyond a rapidly beating heart.

On physical examination there was dullness with tubular breathing and râles at the right apex. Although she said that she had no chronic cough, yet on persuasion it was possible for her to raise sputum containing tubercle bacilli. The roentgen-ray revealed an area of infiltration involving the right upper lobe in the midst of which was a small circular area of decreased density suggesting cavitation.

This case represents chronic tuberculosis beginning insidiously and becoming well advanced before it is recognized. It is a clearly defined typical picture. To me, however, the most important features of this particular case are its subsequent course, and the fact that a good family doctor could have been so helpful. The patient was sent to a sanitarium where the authorities said that after six months she would be well. At the end of this time, however, she was transferred to another sanitarium for another six months. Here she met a young man whom she married.

She appeared to get along splendidly, she was discharged from the sanitarium well, and four years later had a baby. But nine years after her first appearance in our Clinic, when the baby was five years old he developed tuberculosis and his mother began again to have a slight afternoon temperature. An alert family physician might well have been the one to advise her in regard to such matters as marriage and pregnancy, to follow up her case, to keep her under supervision and to outline the proper plan of life for her. As it was, the tuberculosis specialist gave her admirable hospital care, yet after she left the sanitarium, neither he nor any one else was concerned with her method of living, and the end-result was a preventable medical calamity. There are too many cases of this description which keep cropping up year after year in all our hospitals.

A nurse, 25 years old, entered the Hospital in December 1922, with a left-sided pleural effusion. The chest was tapped, and the fluid inoculated into a guinea pig with negative results. Because of the probability that the pleurisy was tuberculous, she was kept at rest for six weeks. At the end of that period, her physical signs were negative, a roentgenogram of her chest showed no positive findings, and gradually she was allowed to resume her work.

About six months later she reentered the Hospital with a second attack of pleurisy with effusion, the right chest now being involved. This chest was tapped, the fluid inoculated into a guinea pig, and on this occasion the diagnosis of tuberculosis was established. The patient was sent to a sanitarium where she remained for two years. At the end of this time roentgenograms and physical examination were negative, but the tuberculin fixation test was positive. She was regarded as having tuberculosis.

After leaving the sanitarium she worked for a little over a year. Then she

began to feel too easily tired, to lose a little weight and to be conscious of a rapidly beating heart. There was dullness at both apices with a few persistent crackling râles. Roentgenograms revealed a small but definite area of infiltration in the left apex. She rested for several months and then having gained weight and strength, went to Florida where she obtained an easy job.

This patient felt well until 1928—six years after her original illness. Then, once more, she began to tire easily, to feel conscious of her heart, and to lose weight. There were râles at both apices. Roentgen-ray films revealed fairly extensive bilateral infiltration in both upper lobes. Since then she has gone down hill gradually, has developed cavitation in a slowly spreading process and for more than a year has been bed-ridden.

This case, followed over a ten-year period, illustrates two points: the importance of pleurisy with effusion and the relentless advance of pulmonary tuberculosis in certain individuals.

Pleurisy with effusion is seen not uncommonly in general practice. It should be regarded, always, as being due to tuberculosis. In the Peter Bent Brigham Hospital for many years Professor Christian has advocated immediate withdrawal of the fluid from the affected chest. The procedure is a simple one. The fluid does not tend to recur, and its removal not only makes the patient's breathing considerably easier but also shortens the febrile response to the disease. The immediate treatment of pleurisy with effusion, therefore, is simple.

The follow-up treatment of pleurisy with effusion is more complicated. Patients with this disease should be kept at rest for long periods of time, should have periodic reexaminations, and should be taught to take care of themselves with the same meticulous regard for detail as with an open lesion. One can never tell when the original focus may flare up into an actively spreading process. The prevention of such an accident lies in the hands of the family physician.

Of the relentless advance of tuberculosis there is little to say except that it occurs under the best of conditions. In this connection, however, I have been struck by the number of people with tuberculosis who have come to the Peter Bent Brigham Hospital, and who have been transferred later to tuberculosis hospitals in various parts of the country, whose relations have kept returning to our house officers or staff for subsequent advice involving such questions as the following: Should the sanitarium doctor be allowed to inject air into the patient's chest or to do a more radical operation? Is hemoptysis an ominous sign? How long shall the patient stay in bed, and is the sanitarium doctor right in allowing the patient to get up so soon? Is it proper for the sanitarium doctor to have the patients' tonsils removed? Does the sanitarium doctor know what he is doing? Questions of this sort, propounded by patients' relatives, have made me feel that the family doctor should occupy a very important strategic position in the management of tuberculosis, between the patient on the one hand and the sanitarium on the other. He can be a very helpful *liaison* officer. The tuberculosis specialist takes care of the patient during an acute phase of a chronic disease.

whereas the family physician should take care of the patient during his entire lifetime. Therefore, unless the general practitioner knows what is going on in the progress of medical knowledge of tuberculosis so that he has an intelligent opinion in regard to new therapeutic methods, unless he can take care of his tuberculous patients after they are discharged from various special hospitals and can observe their lesions intelligently, he is not practicing good medicine and is missing an important chance for doing constructive medical work. It is fully as interesting and important for a doctor to make sure that a quiescent tuberculosis remains inactive as it is for him to become trained in such procedures as the technic of artificial pneumothorax.

A 30 year old man entered the Hospital in September 1926. As a boy he had suffered from occasional attacks of dry pleurisy, but these had not been at all disabling. He had a good war record and was not ill during his experience in France. He had spent the year previous to coming to the Hospital in London, where he had been studying, and when he set sail for America in late August he felt as well as possible. On the ocean he seemed a little out of sorts, but attributed this to mild sea-sickness. Shortly after landing he had a sudden attack of pain in the right lower chest, aggravated by deep breathing and accompanied by a low fever, a pleural rub, and later by physical signs of slight hydrothorax. He did not improve, the fever persisted, roentgenograms of the chest revealed a fine diffuse mottling through both lung fields, he began finally to raise sputum and to pass urine and feces which contained tubercle bacilli, and at last he developed the clinical picture of a terminal meningitis. He died about three months after he first began to feel unwell. The necropsy revealed a generalized military tuberculosis with involvement of almost every organ.

Miliary tuberculosis occurs in general practice rarely, so that it is often forgotten and therefore not suspected, under any circumstances it well may afford a baffling diagnostic problem. The description of miliary tuberculosis which appeared in the first edition of Osler's Practice forty years ago has not been improved on by anything written in our more modern textbooks. Osler reminds us that there are chiefly three clinical forms of generalized tuberculosis: the typhoid form with the symptoms of an acute general infection, cases in which pulmonary symptoms predominate, and cases in which the cerebral or cerebrospinal symptoms are marked. In the typhoid form—which seems to me to be the one most difficult to recognize—the patient presents the symptoms of a profound infection which simulates and is frequently mistaken for typhoid fever. Osler points out a differential point well worth remembering: namely, that the greater frequency of the respirations and the tendency to slight cyanosis are much more common in tuberculosis. He reminds us that in general tuberculosis the spleen may be enlarged—but not as early or as markedly as in typhoid—and that reddish spots on the skin may develop which can be confused with rose spots. There is no special treatment and the prognosis usually is hopeless. However it is worth remembering that occasional cases recover. A few years ago Professor Christian had a negroess¹ in his wards at the Peter Bent Brigham Hospital with military tuberculosis as demonstrated by find-

ing the histologic picture of tuberculosis in one of the skin lesions which developed, as well as by typical roentgen-ray films of her chest. She ran a protracted febrile course for many months but eventually got well and still shows herself in our Out-Door Department from time to time to prove the tale.

In my experience with our medical students, tuberculosis, I am glad to say, has appeared very infrequently. When it has appeared, it has shown up unexpectedly, in boys previously supposed to be perfectly healthy, and with symptoms simulating an acute upper respiratory infection, or as a sudden hemoptysis.

In 1927, a robust-looking young man went away on a vacation. He was in good condition so far as he knew. He played a violent game of tennis one morning and immediately after it, began to raise large quantities of bloody sputum. When he was admitted to the Hospital he looked critically ill. Over the right upper lobe were râles, and exaggerated voice and breath sounds. Roentgenograms of the chest showed marked infiltration through both lungs suggesting an acute bronchopneumonia. The sputum contained tubercle bacilli.

He was put to bed. The temperature quickly fell and within two weeks was entirely normal. The cough disappeared, the râles and signs of consolidation cleared up rapidly and no more sputum was forthcoming. He was able to return to work within a year following the hemoptysis and has been well and active ever since.

Cases of this type are encountered from time to time, and are always at first seen by the family doctor. At the onset they look as though their outlook might be hopeless and yet they may run a very benign course. The roentgen-ray picture often appears to show a much more extensive lesion than actually is present, due, apparently, to hemorrhage infiltrating the lung. In fact, not infrequently, the patient whose tuberculosis becomes manifest by a pulmonary hemorrhage is the lucky one, for the diagnosis is established immediately and proper treatment is instituted without waste of time.

These instances, perhaps, are sufficient to illustrate the growth of my feeling in regard to the tuberculosis problem. Other individual cases keep coming to mind—a case for instance of old, supposedly healed tuberculosis which became fatally activated by a surgeon's injudicious use of ether without the family doctor's consent, a case of quiescent tuberculosis brought to life by the uncontrolled use of the Alpine lamp when it was the latest fashion, a case of tuberculous empyema recognized and saved from improper surgical treatment. In brief, as I have seen pulmonary tuberculosis, not as a specialist, but as an individual engaged in more general medical work, I have acquired gradually certain very definite convictions in regard to it. Pulmonary tuberculosis is still so common a disease as to be ever-present, and general practitioners are seeing it frequently, perhaps failing to recognize its significance. All must learn to make the diagnosis at the earliest possible moment, and must take an increasing responsibility in learning how to treat it to best advantage. The treatment of tuberculosis while it is acute, will probably and properly continue in the hands of well trained

specialists After the acute stage is over, when the disease has become quiescent, the majority of cases will return to the hands of their family doctors The family doctor, therefore, must take an increasingly active part in the campaign against tuberculosis in order to prevent the occurrence of such common catastrophes as I have outlined

REFERENCE

- 1 MARLOW, F W, JR Military tuberculosis of lungs with recovery, report of 2 cases, *Am Rev Tuberc*, 1929, xix, 529-543

A GRAPHIC STUDY OF THE CHANGES IN THE MUSCULAR ACTIVITY OF THE STOMACH ASSOCIATED WITH CERTAIN EPIGASTRIC SYMPTOMS *

By P B WELCH, M D , F A C P , *Coral Gables, Florida*

SOME years ago (1924) while the effect of feeding upon the muscular activity of the colon was being studied,¹ it seemed that a similar investigation of the muscular activity of the stomach might satisfactorily explain the almost constantly presented symptom of epigastric distress, the distress usually described by the patient as "gas" A perhaps cursory survey of the literature failed to supply any satisfactory physiopathologic explanation of the association of this symptom complex with so many different kinds and gradations of abdominal pathologic lesions or disturbed functions

It seemed opportune to make a beginning at least by recording exactly what changes in muscular activity were occurring in the stomach during these so called "gas" attacks Accordingly, such an investigation was undertaken

Kymographic tracings were made of the muscular activity of the stomach both in health and in the presence of varying abdominal symptoms and lesions The tracings were obtained by placing a condom balloon of known capacity into the fasting stomach The balloon was connected by means of a Rehfuß tube to a pear flask which was partially filled with water, leaving an air space above the fluid level This air was in turn connected to a Brodie recording bellows² which recorded upon a slow speed kymograph

These experiments were invariably begun upon a fasting stomach (14 to 18 hours) with the patient in a comfortable reclining position The height of the pear flask containing water and air was adjusted to develop only sufficient hydrostatic pressure to gently distend the balloon in the stomach

After insertion of the balloon it was left in place long enough for the patient to become accustomed to the presence of the small Rehfuß tube and for the stomach to become accommodated to the presence of the balloon The movements of the fasting stomach were then recorded When the typical hunger contractions, described by Carlson³ and others, were present the patient while still reclining was hand fed The feeding consisted of cereal and milk, or milk and graham crackers The patient remained relaxed and did not lift the head during the feeding This precaution was necessary to avoid any increase in intra-abdominal pressure

Tracings were continued for a period of three to seven hours, usually lasting two hours after the feeding By prolonging the tracings after feeding it was possible to have a record of the digestive cycle of the stomach The abnormalities of gastric motility naturally developed consecutively dur-

ing this period, duplicating the condition producing the symptoms in each case

A series of 16 tracings was made on humans who had clinical evidence of some abdominal disturbance. Tracings were made on normal humans and on dogs (figure 1) with permanent gastric fistulae. These latter were

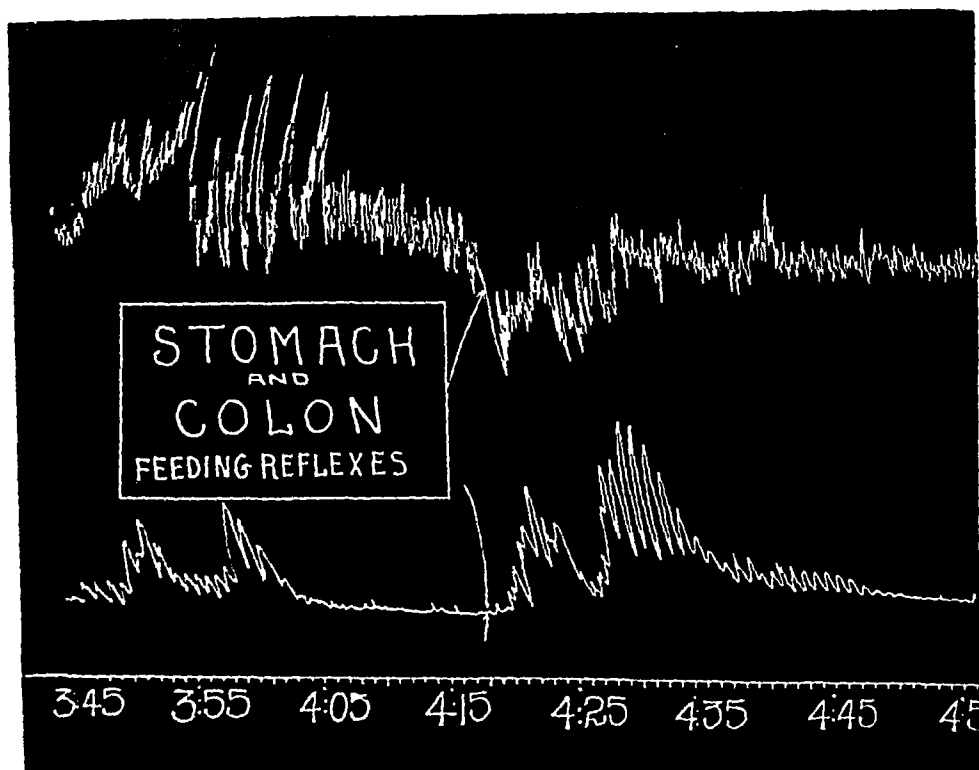


FIG 1 Simultaneous tracings from stomach and colon of dog with permanent gastric and colon fistulae, showing normal inhibition and relaxation of the muscular activity of the stomach at the time of feeding. Lower tracing shows normal increase in muscular activity of colon in response to feeding.

made as controls and completely corroborated the work of Carlson⁴ and others who found that normally hunger contractions of the stomach are inhibited and gastric muscular tone is lowered upon the taking of almost any kind of foodstuff into the mouth. Indeed even indifferent substances such as paraffin were shown to produce a similar though fleeting effect. This reflex is doubtless an appetite or taste reflex similar in its production to that seen in the colon.¹

In 14 of this series of 16 cases the normal immediate inhibition was not only absent but reversed. Usually upon the first taste of food there was an immediate and sometimes amazing increase in muscular tone of the stomach. Some of these marked inversions actually emptied the balloon almost completely indicating a virtual obliteration of the gastric lumen. Usually there was an associated inhibition of peristalsis but not invariably so. Figure 2 shows a well marked inversion of the taste reflex.

There did seem to be some quantitative relationship between the intensity of the symptoms and the degree of inversion as shown by comparison

of figures 2 and 3, the latter showing a moderate inversion with moderate symptoms associated with an irritable colon, as compared to figure 2 with rather intense symptoms and a marked inversion associated with a chronic appendicitis

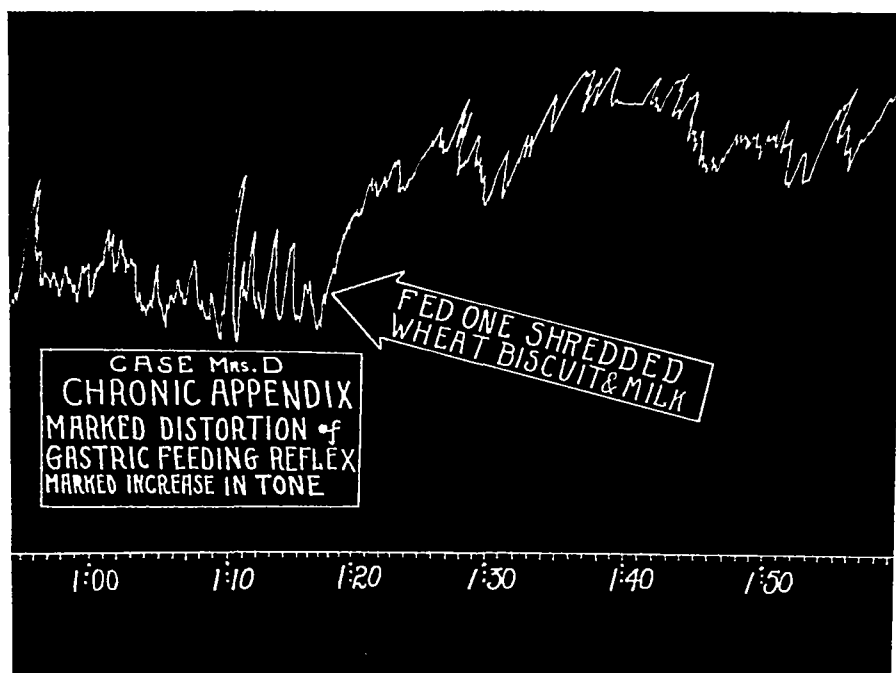


FIG 2 Tracing from human stomach (Case No 1) showing marked inversion of the feeding or taste reflex associated with chronic appendix with strong sensory stimuli

Table 1 correlates the diagnosis, character and intensity of symptoms and degree of inversion of the reflex. In every instance where the sensory stimulation was strong there was a very marked disturbance of muscular activity. In four instances the sensory stimulation was apparently stronger than the inversion, probably due to the patient's susceptibility to sensory stimuli.

In table 2 are grouped those 10 cases in which fractional gastric analysis was done.

In five instances there was a complete achlorhydria. Two of these showed a normal gastric taste reflex. In both these instances the tracings were made because of the absence of hydrochloric acid. In one case the patient was symptom free. The other had been under treatment for a month for gastric atony and achlorhydria. In this group of five cases the absence of free hydrochloric acid apparently had no influence upon the muscular activity of the stomach. The same may be said of those classified as hypochlorhydria and hyperchlorhydria.

It has long been known that chronic appendicitis, gall-bladder disease and other abdominal visceral diseases produce reflex spasm of the pylorus. Carlson and Litt⁵ pointed out that "motor disturbances of the pylorus may

T A B L E I
Correlation of the Diagnosis, Intensity of Symptoms and Degree of Inversion of the Reflex

	Diagnosis	Abdominal symptoms	Symptom intensity	Degree of inversion
1	Chronic appendicitis	Post prandial epigastric distress also right upper quadrant distress	4+	4+
2	Chronic appendicitis	Post prandial epigastric burning eructations	2+	3+
3	Chronic appendicitis, duodenal ulcer	Post prandial epigastric pressure eructations abdominal soreness	3+	4+
4	Chronic appendicitis, duodenal ulcer	Post prandial epigastric distress right lower quadrant soreness	3+	3+
5	Duodenal ulcer	Epigastric soreness eructations	3+	4+
6	Chronic duodenal ulcer, moderate stenosis	Soreness l u q eructation occasional vomiting	3+	4+
7	Simple gastric ulcer, prunitus ani, achlorhydria	Epigastric fullness and soreness—eructations	1+	3+
8	Colon stasis, irritable colon, over-eating	Epigastric pressure, eructations	2+	2+
9	Hypertrophic hepatitis	General epigastric pain—eructations	4+	4+
10	Glossitis subacute hemorrhoids, irritable colon	Epigastric burning	3+	2+
11	Gastric neurosis, colon stasis, achlorhydria	Epigastric burning, pressure and eructations	3+	2+
12	Pernicious anemia, irritable colon, achlorhydria	Epigastric gnawing pain	3+	1+
13	Marked colon stasis, irritable colon	Epigastric gnawing pain	1+	1+
14	Hemorrhoids, irritable colon, marked stasis	Epigastric fullness and pressure	2+	1+
15	Achlorhydria, gastric atony	Symptom free	-	None
16	Achlorhydria	Symptom free	-	None

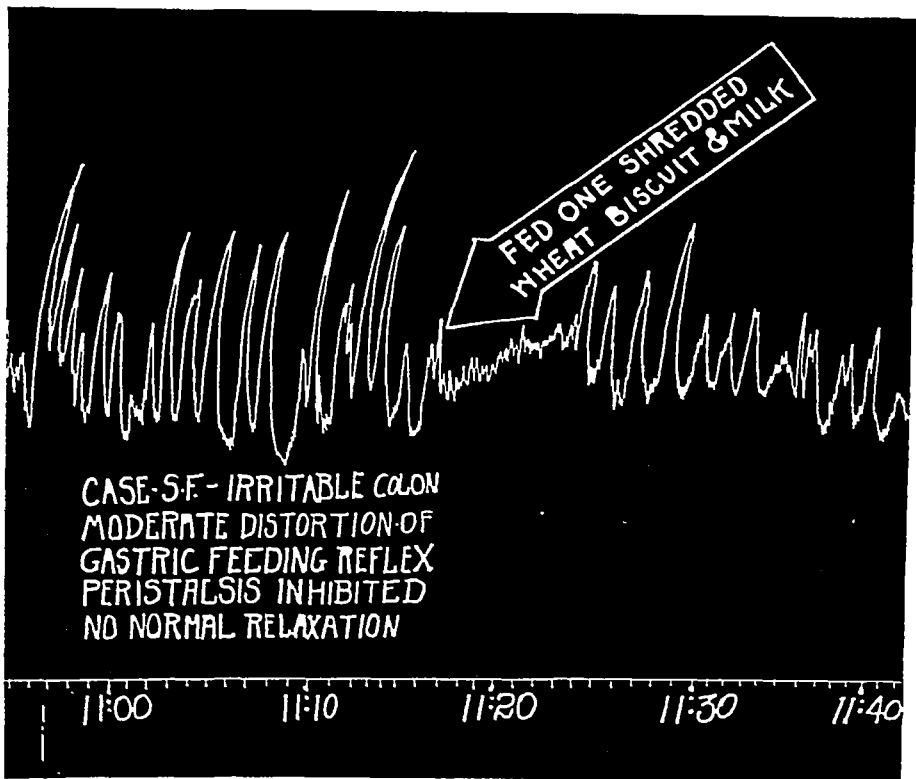


FIG 3 Tracing from human stomach (Case No 13) showing moderate inversion of the feeding or taste reflex associated with an irritable colon with moderate sensory stimuli

be induced ' ' by excessive irritation of most, if not all, sensory nerves, particularly those of the abdominal viscera "

The work done in this series would seem to indicate that excessive stimulation of the sensory nerves, of the abdominal viscera at least, causes reflex motor disturbances not only of the pylorus but also of the rest of the gastric musculature

The chief purpose of this presentation has been to show that a relationship exists between the symptom complex commonly complained of as "gas" and certain departures from the normal muscular activity of the stomach consisting of a reversal of the normal taste reflex

While the number of experiments in this series is perhaps too limited to permit of any generalizations, it does seem justifiable to draw certain tentative conclusions which may prove helpful in the interpretation of certain symptoms which daily are presented to the gastroenterologist and to the general practitioner.

CONCLUSIONS

1 There exists a definite etiologic relationship between the symptoms of epigastric distress, fullness and pressure, and muscular spasm of the stomach upon the placing of food in the mouth

2 This spasm is a reversal or inversion of the normal appetite or taste reflex and consists of an increase in gastric muscular tone instead of relaxation and inhibition

TABLE II

Showing Gastric Analysis in Ten Cases and Degree of Inversion of the Feeding or Taste Reflex, There Apparently Being No Relationship between the Degrees of Acidity and the Inversion of the Reflex

		Degree of acidity					Degree of inversion
		Fasting	30 min	60 min	90 min	120 min	
Case 11	Free acid	0	0	0	0	0	None
	Total acid	50	44	36	32	28	
Case 12	F	0	0	0	—	—	2 +
	T	28	44	50			
Case 13	F	0	0	0	0	0	1 +
	T	—	20	20	28	40	
Case 14	F	0	0	0	0	0	None
	T	—	30	54	56	54	
Case 7	F	0	0	0	0	0	3 +
	T	—	—	—	—	—	
Case 2	F	0	0	0	10	26	3 +
	T	44	70	68	92	90	
Case 6	F	0	0	0	0	38	4 +
	T	26	30	30	26	90	
Case 4	F	50	36	44	60	56	2 +
	T	80	66	94	120	92	
Case 3	F	80	12	0	0	0	4 +
	T	138	36	30	38	42	
Case 5	F	102	56	50	86	76	4 +
	T	136	106	88	118	118	

3 There is an apparent quantitative relationship between the intensity of sensory stimulation and the degree of inversion of the appetite reflex

4 These sensory stimuli may be intra- or extra-gastric in origin

5 The inversion of the appetite reflex is apparently independent of the secretion of hydrochloric acid, being apparently purely a motor phenomenon

REFERENCES

- 1 WELCH, P B, and PLANT, O H A graphic study of the muscular activity of the colon, with special reference to its response to feeding, *Am Jr Med Sci*, 1926, clxxii, 261-268
- 2 BRONF, T G On recording variations in volume by air-transmission A new form of volume-recorder, *Jr Physiol*, xxvii, 473-487
- 3 CAPISON, A J Control of hunger in health and disease, 1916, University of Chicago Press, Chicago, p 28
- 4 CAPISON, A J Control of hunger in health and disease, 1916, University of Chicago Press, Chicago, pp 164-165
- 5 CAPISON, A J, and LITT, S Studies on the visceral nervous system on the reflex control of the pylorus, *Arch Int Med*, 1924, xxviii, 281-291

THE RELATIONSHIP OF THE AUTONOMIC NERVOUS SYSTEM TO GENERAL MEDICINE*

By THOMAS P SPRUNT, M D , F A C P , *Baltimore, Md*

PROFESSOR CANNON has clearly and concisely outlined the marvelous biological mechanisms by which the fluid matrix of the body is preserved in healthful equilibrium and by which its remarkable reserve forces are mobilized and made available for extraordinary activities. The autonomic nervous system is among the most important mechanisms in the preservation of this homeostasis that Cannon has poetically dubbed the wisdom of the body. One might, then, readily expect that this system would play an equally important rôle in the manifestations of the folly or of the unhappiness of the body that constitutes disease.

As in the preservation of homeostasis in health it is often impossible to differentiate sharply between the effects of nerve impulses and of humoral activities, so under pathological conditions we not infrequently must consider a maze of inseparable effects produced by nerve impulses, by hormones, and by other chemical agents. It is well to keep this fact constantly in mind in any consideration of the part played by the autonomic nerves in disease processes.

The autonomic or the vegetative nervous system is divided anatomically and physiologically into two definite systems, namely the sympathetic division or thoraco-lumbar outflow and the parasympathetic or cranio-sacral outflow. Of these, the parasympathetic system seems designed especially for individual organ effects and subserves a group of reflexes chiefly protective, conservative, and upbuilding in their service. The sympathetic division on the other hand is well adapted to the exercise of general and widespread activities and has much to do with the preservation of homeostasis or the prevention of serious changes of the internal environment both during ordinary activities and under conditions of stress. Where these two systems send fibers to the same organ as they do in the case of most of the viscera, their activities are usually antagonistic to each other, the one exciting and the other inhibiting the secretion or the motility of the viscus, hence when the nervous relationships to an organ are known one can generally recognize a symptom on the part of the structure as of sympathetic or of parasympathetic origin.

AUTONOMIC NERVOUS REFLEXES IN ORGANIC DISEASE

It is as a mechanism for the development of symptoms and signs in organic disease that I would first stress the activities of the autonomic

* Read before the American College of Physicians Montreal, February 9, 1933

nerves Autonomic symptoms may arise by reflex action from a stimulus in any part of the body or by the effects of humoral agents upon centers in the central nervous system They may be inaugurated by a great variety of stimuli An important factor in many or in all cases is the constitution of the patient, for in one person a given stimulus may be adequate to produce a symptomatic effect whereas in another person the same stimulus may be without such effect Some years ago the Viennese clinicians, Eppinger and Hess, announced their conviction that certain people were constitutionally predisposed to parasympathetic symptoms while others were prone to the development of symptoms due to sympathetic activities Of the pharmacodynamic agents that were developed for testing such potentialities, adrenalin was used to test the sensibility of the sympathetic nervous system while pilocarpin was used as a stimulant for the parasympathetic system, and atropin as an inhibitor of its action Most of the more recent workers in this field are agreed that sharp differentiation between sympathicotonic and vagotonic states and constitutions are not practicable nor in accord with the available data Nevertheless, this conception has been a great stimulus in the study of the symptomatology of disease

The reflexes by which symptoms arise are of different complexity, varying from the simplest axone reflex, through the ordinary spinal reflex, to much more complicated pathways including a number of intercalated neurones on the afferent side, a participation of several centers in the central nervous system, and an outflow through different efferent channels A gastric ulcer may serve as a stimulus in a relatively simple reflex producing hypersecretion and hypermotility of the stomach An inflamed appendix or gall-bladder may reflexly produce the same phenomena in the stomach How frequently the patient with early pulmonary tuberculosis complains of a prolonged cold in the head or of gastrointestinal symptoms Viscero-motor reflexes may originate from a stimulus within a viscus and affect the skeletal musculature overlying that organ In the case of the so-called viscerosensory reflexes the stimulus again arises within the viscus and its effect is the referred pain to the body wall that may be so helpful as a diagnostic sign As there are many reflex arcs from organ to skin (viscero-cutaneous reflexes) so there are reflexes from skin to organs (cutaneo-visceral reflexes), the latter forming the basis for much that is most useful in our methods of physical therapy Such manifestations of pathological physiology in the autonomic nervous system are of daily use to us in diagnosis, in prognosis and in therapy

In certain types of diseases, as for example, in exophthalmic goiter and other endocrinopathies, and in the manifestations of allergic phenomena, autonomic disturbances are particularly prominent Again, they predominate in certain paroxysmal syndromes like epilepsy, migraine and the vascular crises that occur in different regions of the body In his analysis of important symptoms of early tuberculosis, Pottenger lists as due to visceral reflexes hoarseness, tickling in the larynx, cough, digestive dis-

turbance (hypermotility and hypersecretion), circulatory disturbance chest and shoulder pains, flushing of the face, spasm of muscles of the shoulder girdle and diminished motion of the affected side. Similarly, in the analysis of symptoms of any important organic illness, one may find evidence of many reflex disorders and realize how richly the visceral nerves contribute to the symptomatology of structural disease.

THE AUTONOMIC NERVOUS SYSTEM AND FEVER

There exists in fever an interesting example of the interrelationship of the autonomic nervous system with a fundamental symptom of a large group of diseases, and the current interest in this relationship justifies some detail in its consideration. There is reason to believe, of course, that fever is one of the protective mechanisms of the body, that it may inhibit the growth of certain thermolabile organisms, that it may heighten the production of immune antibodies, and that it may be of protective service in other ways.

That the autonomic nervous system plays a rôle in heat regulation and also in the production of fever is indicated by abundant data. It has been amply demonstrated by pathologists and by neurological surgeons that tumors and other lesions in the diencephalon and in the walls of the third ventricle, as well as operative traumata in these regions, are sometimes attended by marked hyperpyrexia. On the other hand, heat regulation is decidedly disturbed and fever cannot be experimentally produced in animals whose sympathetic nervous systems have been removed or whose cervical cords have been severed. Cannon's sympathectomized cats could not maintain a normal temperature in a cold room and his sympathectomized monkey suffered a sun-stroke when placed out of doors on an ordinary summer day. From a clinical standpoint Gordon Holmes has reported among his patients with acute war injuries to the spinal cord a series of 10 cases with extensive lesions at the cervical enlargement that showed a remarkable clinical picture characterized by subnormal temperature, slow pulse, low blood pressure, a scanty secretion of urine, and a stuporous or extremely lethargic mental state. The body temperature was as low as 80° F.

Although the participation of the autonomic nervous system is recognized we have but little satisfactory understanding of the manner in which fever is produced. It seems altogether probable that the difficulty lies not so much in an overproduction of heat as in a disturbance of its elimination. Although the very marked increase in the heat production of exercise is compensated by an equivalent heat loss so that no sustained rise of body temperature occurs, the relatively small increase in heat production in fever is not so accurately compensated. Clinically we may watch the mechanism at work in the acute onset of fever with a chill. There is marked peripheral vasoconstriction, the skin is dry and cold, gooseflesh appears. The patient feels cold, shivers and shakes, covers himself with blankets and although his sensation of cold continues the body temperature is at its highest during

the chill. Other reflex mechanisms may play a part in the increased body temperature.

In his study of the skin temperatures of children Talbot was impressed with the importance of the skin of the arms and legs in the conservation or dissipation of body heat. He found that during fever the reaction of the skin to surrounding temperatures, changes definitely when the temperature of the body reaches approximately 39°C . At this point some fundamental change takes place in the physiology of heat excretion.

When we consider conversely the influence of fever upon the autonomic nerves it is of course often difficult to differentiate between the effect of the fever itself and that of the toxins that produce it. The induction of fever by physical methods has shown that many of these effects are due to the elevation of temperature per se. As Talbot has indicated, at a certain level of temperature a change occurs in the skin of the extremities and in the dilatation of the cutaneous vessels. This is in apparent harmony with a general change of tone in the vegetative nervous system in fevers. Beaumont, in 1833, recorded a decrease in the gastric secretion in febrile states, a fact that has been confirmed by many clinical observers. The fact has also been demonstrated in Pavlov pouch dogs that increased body temperature itself, apart from any possible action of bacterial toxins, depresses the gastric glands. It is a matter of clinical observation that conditions like asthma, paroxysmal tachycardia, and gastric crises that are totally or in part produced by mediation of the vegetative nervous system may be greatly ameliorated when the patient has a febrile illness. Danielopolu has recently called attention to this fact and to what he considers the similarity in the effect of fever and of anesthetics upon paroxysmal syndromes. He believes that both with fevers and with anesthesia there is a modification of the autonomic tone and he affirms that if we follow daily the state of the vegetative system after anesthesia we see that the vegetative tone is not restored for the most part very rapidly but that there is necessary a certain time, several days to several weeks, before the normal tone is fully recovered. He believes that it is common during febrile attacks for such paroxysmal syndromes as those mentioned above to disappear temporarily, to return at a variable period after the fever is gone. He studied the state of the vegetative nervous system during an epidemic of typhus fever and found that doses of adrenalin that ordinarily produced an effect must be increased very markedly during the fever in order to encompass a similar effect. The more severe the fever and the toxemia, the more slowly does this test return to normal after the febrile period.

The influence of fever and of anesthesia on the autonomic nerves is well exemplified in the case of the vasoconstrictors of the extremities, and this fact has been put to definite and practical use in the differential diagnosis and in the therapy of peripheral arterial diseases. A study of the vasoconstrictor gradient or of the vasomotor index is now an essential step in the determination of the type of therapy to be used even in the pre-arrest, circulatory conditions.

The recently devised methods for the induction of fever by electricity offer a new opportunity for the study of its possible effects upon autonomic nervous mechanisms

THE DIENCEPHALIC CENTERS AND METABOLISM

Earlier students of the autonomic nervous system thought of centers for its reflexes only in the spinal cord. Later, centers in the medulla were recognized and still more recently the diencephalon has been subjected to intensive study. The diencephalon is that small portion of the interbrain laid down early in phylogenetic history and situated between the hypophyseal stalk and the floor of the third ventricle. Beattie, Cushing, Biedl and their collaborators have been particularly active in studying the interrelationship of the diencephalic centers with the posterior lobe of the hypophysis on the one hand, and with the thalamus and the cerebral cortex on the other hand. The confirmation and acceptance of these studies will afford a welcome correlation of conflicting opinions concerning the relative importance of the posterior lobe of the hypophysis and of the adjacent nerve tissues on water metabolism (diabetes insipidus), fat metabolism (cerebral adiposity or emaciation), disturbances in heat regulation, in basal metabolism, and in other phases of metabolic activity.

In this hypothalamic region three cellular areas in general are described, an anterior or supraoptic nucleus, the median or tuberal collections in the tuber cinereum, and the posterior or supramammillary center. From these areas, and particularly from the first two, there are described nerve fibers passing downward, becoming concentrated in the stalk of the pituitary and distributed throughout the posterior lobe to its epithelial investment. There are two views concerning the mechanism by which the posterior lobe and pars intermedia may affect these hypothalamic centers, first, the possible passage of the secretion through the tissues of the posterior lobe and infundibulum into the third ventricle, and second, a vascular mechanism described by Popa and Fielding as a "portal" circulation through which the venous blood from the pituitary passes into the tuber cinereum and bathes the tuberal nuclei. Cushing and Beattie believe, partly on an anatomical basis, and from the results of electrical stimulation, partly on the basis of pharmacodynamic studies by the injection of pituitrin and of pilocarpin into the cerebral ventricles, that the supraoptic nucleus and the tuberal nuclei subserve parasympathetic impulses and that the posterior diencephalic center is connected with the sympathetic outflow. Upon the integrity of the posterior nucleus depends the "sham rage" (a typical sympathetic storm) in decorticated animals described by Cannon and by Bard. The further possibility has been suggested that the posterior lobe of the hypophysis may bear the same general relationship to the parasympathetic nervous system that the medulla of the adrenal gland bears to the sympathetic division.

Josefson has reported the case of a man, aged 32 years, who presented

the following clinical features emaciation, anorexia, weakness, mild somnolence, a brief phase of polyuria and polydipsia, dryness of mouth and throat, feelings of cold, falling out of hair of scalp and loss of body hair, changes in nails and teeth, loss of libido and potentia, dizziness, depression, occasional headaches, achylia gastrica, retarded basal metabolic rate (minus 23 per cent), arterial hypotension (85/60), and hypoglycemia. At the autopsy a small tumor of hazel nut size was found in the diencephalon in the region of the mammillary bodies. The viscera were of small size and the endocrine glands especially were atrophic, including the hypophysis which, however, was normal on histological examination. The ribs were thin and fragile.

We have recently studied a similar case but without the opportunity of an anatomical examination.

It is of great interest that so many symptoms and signs usually attributed to primary endocrine dyscrasias seem in this case to be due to a small lesion in that part of the brain, the site of the most important centers of autonomic nerve impulses. One may conjecture concerning a possible secondary rôle played by the hormones.

PSYCHIC INFLUENCE UPON THE AUTONOMIC NERVOUS SYSTEM

The close anatomical relationship of these centers in the diencephalon with the thalamus, where resides the central mechanism for the integration of the emotions, and with the cerebral cortex, the seat of the higher intellectual powers, suggests at once an anatomical basis for the well known effect of psychic processes upon the autonomic nervous system and through it upon the normal and the pathological physiology of the viscera. Cushing says in regard to the diencephalon: "Here in this well concealed spot, almost to be covered by a thumb nail, lies the very mainspring of primitive existence, vegetative, emotional, reproductive, on which, with more or less success, man chiefly has come to superimpose a cortex of inhibitions." In this region too are hidden some of the mysteries of the rhythm of the body, including the mystery of sleep, the changes in the autonomic nervous system that occur in sleep and the similar changes in hypnotic states.

The physiologists, Pavlov, Cannon, Carlson, and others, have abundantly shown the influence of psychic processes upon the vegetative system under normal and under abnormal conditions. When one understands the readiness with which lower animals may be conditioned to unusual autonomic reflexes he can the more easily appreciate the large part that conditioned reflexes must play in the life of man, in his usual behavior as well as in his neurotic reactions. Often the conditioning stimulus may have been more or less obscured by time and by superimposed events. Vegetative phenomena of psychic origin may complicate organic disease and they may play a conspicuous part in the symptomatology of a neurosis.

In the disharmony of nervous function that is a neurosis, or the expression of a vital conflict, the inherited material or the constitution of the

patient plays a major rôle. Most or all of us doubtless react at some time to our conflicts in a neurotic manner but the majority, by reason of sufficiently stable constitutions, escape a major neurosis. In those persons sufficiently predisposed we see the development of affective disorders, of hysteria, of psychoneurotic states, with any of which there may occur more or less widespread and distressing participation of the autonomic nervous system, with feelings of tension, with headaches, respiratory symptoms, cardiac disturbances, gastrointestinal derangements, peripheral vasoconstrictions, endocrine imbalance, and metabolic changes. Although the emotions cannot be weighed or accurately measured, the autonomic effect of these emotions, as Emerson remarks, on the glucose tolerance of a previously well standardized case of diabetes, can be measured in terms of grams of sugar in the urine, milligrams of glucose in the blood, and of units of insulin necessary to restore the patient to a satisfactory condition. They may also be measured at times by the difficulty we experience in securing basal conditions for an estimation of the metabolic rate.

The autonomic symptoms in the nervous patient are no less real than vegetative nervous reflexes in the patient with organic disease. The mechanism of the symptomatology in the two classes of patients is very much the same. The stimulus is different, the reflex arcs are different, but the effects may differ not at all and may be even more poignant to the sensitive patient with a functional disturbance. In a neurosis we have not a weakening of nervous function but an increased intensity of reflex activity.

In this connection two interesting questions arise. The psychic phenomena, the emotional stimuli, affect the entire body. What determines the choice of an organ for the manifestation of dysharmony in any given case? Why should this patient with an affective disorder complain of constant nausea, of an aversion to food, and of abdominal pain, and another patient with similar emotional reaction be afflicted with headaches and palpitation? The related question of perennial interest is this: Do functional vegetative disturbances lead to structural organic diseases? In answering the latter question I should say that many of us, I am sure, believe that functional autonomic disorders do eventuate in organic disease. We note the apparent effect of the emotions in the development of exophthalmic goiter, of similar influences in the genesis and in the course of arterial hypertension and its sequelae, in angina pectoris and in bronchial asthma. From Cushing's laboratory recently comes a statement of the relationship of cerebral lesions to gastric ulcers in man and the report of experimental production of erosions and ulcers in animals by stimulation of the vagal centers by intraventricular injections of pharmacodynamic materials. But there is another school of thought ably advocated by Ingvar, who believes that functional nervous states do not cause structural organic disease. He points out the insignificant effects of organic nervous diseases upon the viscera with the exception, in a minor way, of encephalitis lethargica that may give rise to dystrophica adiposogenitalis and to diabetes insipidus. He

speaks of hysteria as the great neurosis and is impressed by the rarity of organ changes in this disease. He says that the experiences of the Great War do not support the idea of a purely psychogenic exophthalmic goiter. He believes that many ailments previously classified with the neuroses have been shown by better diagnostic methods to be really organic diseases. He answers both questions by saying that psychic disturbances affect the entire organism, the excitations go over the whole body, and wherever there is a constitutional inferiority of a tissue or a damaged organ with already a predisposition to irritation, symptoms from that organ become manifest. These organ defects are often latent, in his opinion, and he prefers to think that the organic disease is not caused by nervous phenomena but is really uncovered by them. Although he takes this point of view he does not wish in any way to belittle the importance of the emotions in the course of disease. We may not forget that the body and the mind are one. However we may disagree with his main thesis or with any of his premises, we may well accept his statement that a neurosis is a disorder of the personality, not only the organ affected but the person must be treated. And whoever would undertake to treat the neuroses should do so with a background of thorough knowledge of internal medicine and have every facility at his disposal for the utilization of modern diagnostic methods.

SELECTED REFERENCES

- BARBOUR, H. G., and MARSHALL, H. T. Heat regulation and water exchange, underlying mechanism of fever as illustrated by cocaine poisoned rabbits, *Jr Pharmacol. and Exper Therap*, 1931, *xliii*, 147-162.
- BEATTIE, J. Hypothalamic mechanisms, *Canad Med Assoc Jr*, 1932, *xxvi*, 400-405.
- CANNON, W. B. Bodily changes in pain, hunger, fear and rage, 2d Ed, 1929, D. Appleton and Co., New York and London.
- CANNON, W. B. The wisdom of the body, 1932, W. W. Norton and Co., New York.
- CAPPS, J. A., and COLFMAN, G. H. An experimental and clinical study of pain in the pleura, pericardium and peritoneum. 1932, Macmillan Co., N. Y.
- CAHILL, A. J. The secretion of gastric juice in health and disease, *Physiol Rev*, 1923, *iii*, 1-40.
- CUSHING, H. Reaction to posterior pituitary extract (pituitrin) when introduced into cerebral ventricles, *Proc Nat Acad Sci*, 1931, *xvii*, 163-170, 239-247.
- CUSHING, H. Neuro-hypophyseal mechanisms from a clinical standpoint, *Lancet*, 1930, *ii*, 119, 175.
- DANHOLOFF, D. Action des anesthésiques sur les syndromes paroxystiques qui se produisent par l'intermédiaire du système nerveux végétatif et sur la disparition de ces syndromes pendant les affections fébriles, *Bull et mém Soc méd d hôp de Paris*, 1931, *xliii*, 324-332.
- EVANS, C. P. The importance of the emotions in the etiology and prognosis of disease, *Bull N. Y. Acad Med*, 1929, *v*, 985-1004.
- HUGHES, G. The Goulstonian Lectures on spinal injuries of warfare, *Brit Med Jr*, 1915, *v*, 769, 815, 855.
- JOHANSSON, S. Über zentrale Organkrankheiten, *Acta med Scandinav*, 1931, *lxxv*, 541-562.
- JOHANSSON, S. Zerebrale Mysterien, *Acta med Scandinav*, 1931, *lxxv*, 507-522.
- KRISTENSEN, S. Some disorders of functional origin, *Ann Int Med*, 1932, *v*, 1017-1021.

- KUNTZ, A The autonomic nervous system 1929, Lea and Febiger, Philadelphia
- LIGHT, R U, BISHOP C C., and KENDALL, L G The response of the rabbit to pilocarpine administered into the cerebrospinal fluid, Jr Pharmacol and Exper Therap, 1933, xlii, 37
- LIGHT, R U, and BISSHE, S M The administration of drugs into the cerebral ventricles of monkeys pituitrin, certain pituitary fractions pitressin, pitocin, histamine, acetylcholine and pilocarpine, Jr Pharmacol and Exper Therap, 1933, xlii, 17
- POPA, G T, and FIELDING U Vascular link between pituitary and hypothalamus, Lancet, 1930, ii 238-240
- POTTENGER, F M Symptoms of visceral disease 4th Ed 1930, C V Mosby Co St Louis
- RILEY, H A Migraine, Bull Neurol Inst. N Y, 1932 ii, 429-544
- STRAUSS, I, and GLOBUS, J H Tumor of brain with disturbance in temperature regulation hypothalamus and area about the third ventricle as possible site for a heat-regulating center, report of 3 cases Arch Neurol and Psychiat, 1931, xxv, 506-522
- TALBOT, F B Skin temperatures of children Am Jr Dis Children, 1931, xlii, 965-1052
- ZIEGLER, L H, and LEVINE, B S The influence of emotional reactions on basal metabolism, Am Jr Med Sci, 1925 clxiv 68-76

EDITORIALS

DOCTOR WILLIAM BLAIR STEWART

IN THE early records of the American College of Physicians, under date of December 29, 1916, appears a minute showing that Dr W Blair Stewart was elected to Fellowship at a meeting of the Council at the Astor Hotel, New York City. This was very shortly after the first steps had been taken towards the formation of the College, and at this same meeting the Constitution and By-Laws were adopted and the first regular Officers of the College elected. In the seventeen years that have since elapsed the name of Dr Stewart reappears very frequently in the minutes. From the first he had faith in the future of the College and felt that it was destined both to represent and to serve physicians in the field of Internal Medicine. He identified himself with this purpose of the College and from the time of his election to Fellowship he was a regular attendant at its annual meetings. He was elected a member of the first Board of Governors at the Detroit Clinical Sessions on February 25, 1926, to represent the State of New Jersey. In 1930 he was reelected and unanimously chosen as Chairman of the Board of Governors, and by virtue of that position became ex-officio a member of the Board of Regents. At the expiration of Dr Stewart's second term, which occurred at the recent Montreal Clinical Session, he was persuaded again to accept election for a term of three years and again was unanimously elected as Chairman of the Board of Governors. Those who were present on that occasion will find pleasure in the memory that Dr Stewart in his short address of acceptance was visibly moved by the spontaneous testimonies of confidence and esteem which had accompanied his election.

This long career of service to the College has been brought to a close by Dr Stewart's sudden death. The College has lost one of its most valued officers and innumerable members of the College will feel at future meetings the absence of a friend. His simplicity of manner, his honesty, and his quiet humor drew men to him. Though possessed of sturdy convictions, he was tolerant of the contrary opinions of others. In the chair he maintained the dignity of his office and quietly kept discussion in practical and purposeful channels. Under his wise guidance many problems of the College were brought to a solution. Dr Stewart's generous interests extended in many directions, both professional and civic. His important accomplishments brought him many honors. His duties as a Governor of the College were nevertheless always fulfilled with the utmost thoroughness and promptness. There was no detail concerning the membership from his state but what received his thoughtful consideration.

The spirit and labors of such men as Dr William Blair Stewart have made possible the growth of the American College of Physicians. His loss will be sorely felt. His memory will enrich our traditions.

ENCEPHALITIS

PRIOR to the first waves of the great epidemic of lethargic encephalitis the medical literature contained relatively few references to the non-suppurative inflammations of the brain. Our knowledge of encephalitis, as Zappert has rightly said, falls historically into three periods: before the epidemic, during its height, and since. This third period, which is still in progress, should be of lively interest to the clinician.

It seems probable that since the onset towards the end of the war of the first epidemic of lethargic encephalitis (Economo's disease), the frequency not only of this condition but of other forms of encephalitis as well has been far greater than in former years. Not only have outbreaks been observed of primary encephalitis apparently distinct in type from the lethargic form, but the incidence of the so-called secondary or post-infectious encephalitides has been unusually high. The writings of many experienced clinicians^{1, 2, 3} are in agreement on this point, even though it is realized that allowances must be made for the popularization of knowledge of the condition with consequent freer diagnostic use, and sometimes abuse, of the term encephalitis.

Lethargic encephalitis, though now infrequent, still persists both in the United States and in European countries, and as recently as 1929 a serious epidemic outbreak occurred in Japan. In spite of great activity in research the etiologic agent which causes this disease is still undiscovered, its pathology, however, the clinical features of its course, and its sequelae are fairly well established. While there are many aberrant forms, the disease is especially characterized clinically by the occurrence of the somnolent-ophthalmoplegic, the hyperkinetic, and the amyostatic or Parkinson-like types. The latter are frequently of a slowly progressive character, and may first appear following a latent period of many months after the acute attack. Other typical sequelae are the myoclonic and bradykinetic disturbances of motility, the oculogyric and respiratory tics and the psychic alterations. Pathologically lethargic encephalitis is preeminently a disease of the gray matter manifesting itself in greatest intensity in the midbrain, particularly in the substantia nigra, in the interbrain and less severely in the gray substance about the fourth ventricle. The perivascular infiltrations and other features which characterize its scattered lesions are similar to those found in the focal lesions of poliomyelitis, rabies and Borna's disease in horses.

In addition to this distinctly marked entity, there have occurred in the last fifteen years numerous other types of primary encephalitis, either as sporadic cases or in the form of localized epidemics. Economo² mentions under this heading the occurrence in Australia and in Japan of epidemics of

¹ ZAPPERT, J. Der jetzige Stand der Enzephalitisfrage im Kindesalter, *Wien klin Wchnschr*, 1932, xlv, 737-744.

² VON ECONOMO, C. Gibt es verschiedene Arten von epidemisch auftretenden Encephalitiden oder gehören sie alle zur Encephalitis lethargica?, *Wien klin Wchnschr*, 1931, xlv, 1349-1351.

³ MACNALLY, A. S. Epidemic diseases of the central nervous system, 1927, Faber and Gwyer, London, p. 193.

encephalitis similar to lethargic encephalitis, but showing important differences in distribution of lesions. The singultus epidemics, a small epidemic of neuro-myelitis optica leading in many instances to blindness, and the notable increase in cases of acute disseminated encephalomyelitis are also quoted by this author as evidence of the increased prevalence of non-lethargic forms of primary encephalitis. To these may well be added the small but highly fatal outbreak in New York City of a condition described by Brown and Symmers⁴ as acute serous encephalitis. It is probable that the increased frequency, and at times indeed epidemic character, of so-called serous meningitis⁵ in this country and abroad must be looked upon as a part of this general increase in the primary non-suppurative diseases of the nervous system of the general type of encephalitis.

Many of the conditions mentioned in the preceding paragraph are relatively ill-defined pathologically if not clinically. To some degree, however, acute disseminated encephalomyelitis may be excepted from this statement. With the increased incidence of these cases the clinical and pathological resemblance of this disease to an acute stage of multiple sclerosis has stimulated intensive neuropathological and bacteriological research. Pathologically this form of encephalitis is characterized by rather irregularly distributed areas of demyelination affecting both the gray and the white matter but showing a predilection for the chiasm, the optic tracts and nerves and the subependymal zone adjacent to the walls of the lateral ventricles. The lesions show evidence of a definite inflammatory reaction. This then is a form of primary non-suppurative encephalitis quite distinct in its pathology from lethargic encephalitis which yet has shown, if we may judge from case reports (Redlich⁶), a definitely increased incidence in the last fifteen years.

It is not only in the group of primary encephalitides, however, that a greater frequency of occurrence has been noted. It has long been known that in rare instances non-suppurative encephalitis followed such communicable diseases as measles, chickenpox, smallpox, mumps, whooping cough and scarlet fever. Cases of this type have been reported with such increased frequency in the last decennium as to leave little doubt but what a true increase of incidence has occurred.⁷⁻⁹ The clinical symptoms of encephalitis in these cases may in the acute stage bear a resemblance to lethargic encephalitis. Except in cases of post-measles encephalitis, the course is briefer and the mortality lower. In particular they only rarely manifest the

¹ Brown, C. I. and Symmers, D. Acute serous encephalitis, a newly recognized disease of children. *Am. Jr. Dis. Child.* 1925, xxiv, 174-181.

² Lechner, A., Horstmann, A. and Schürmann, H. Über die Beziehung der Measles zur Enzephalitis bzw. Encephalitis epidemica. *Ztschr. f. klin. Med.* 1921, cxxvii, 68-116.

³ Pott, H. Über eingeleitetes Auftreten von Krankheitsfällen mit den Erscheinungen der Enzephalitis. *Monatsschr. f. Path. u. Neur.* 1927, lxi, 152-184.

⁴ Brown, J. Die post-vakz. Encephalitis und ihre Folgen. *Monatsschr. f. Kinderh.* 1921, xxvii, 24-29.

⁵ Pott, H. W. Über die Enzephalitis im Verlaufe kindlicher Infektionen. *Monatsschr. f. Kinderh.* 1921, cxxvii, 220-271.

late development of such conditions as parkinsonism, or myoclonic residuals. Residual palsies are not infrequent. The pathologic findings are best known in the cases following measles, since in these the mortality is high. The disease in this instance is more truly an encephalomyelitis. Its distinguishing histological features are the presence of perivenous inflammatory infiltrations and of well marked perivascular demyelination. Both the white and the gray matter are involved. These findings differentiate it sufficiently from lethargic encephalitis.

Forms of non-suppurative encephalitis apparently secondary to purulent infections elsewhere in the body, and especially in the head region, have been very frequently reported in recent years, though it is not possible to state definitely that there has been an increase in their incidence. The serous meningitis and the meningo-encephalitis that frequently complicate otitis media⁹ are perhaps the commonest examples of the association to which we refer. Striking clinical types of encephalitis may, however, occur in connection with acute purulent sinusitis¹⁰ and occasional cases seem to be secondary to acute tonsillitis, abscessed teeth, bronchitis, and pneumonia.¹¹ Since the organisms in the primary foci are of pyogenic types while the secondary lesions in the nervous system are non-suppurative, there has developed a tendency for such cases to be referred to as toxic encephalitis. One may place in this same grouping the cases reported as following typhoid fever and dysentery and perhaps the puerperal cases. For the most part the diagnoses of encephalitis, meningo-encephalitis, and encephalomyelitis made in the secondary forms just enumerated are based on clinical rather than pathological criteria.

As further evidence that there has been a general tendency to an increased incidence of all forms of non-suppurative encephalitis, the recent epidemic outbreak of post-vaccinal encephalitis may be cited.¹² Kaiser has found in the literature descriptions of an epidemic of nervous affections following vaccination, which occurred in Bohemia in 1801 and 1802. Since that time, however, no outbreak occurred until 1924. In that year the appearance of cases in England and on the Continent was noted, and up until 1931 when the epidemic was definitely subsiding, over 600 cases had been reported in Great Britain, Holland, Germany, Norway, Austria, and other European countries. In 1928, 1929 and 1930, forty-one cases were observed in the United States. Not only the striking increase in cases, but also the unequal distribution of cases in different communities in the various countries, points toward the true epidemic character of the disease. In one city in the United States there occurred five cases among 5,000 vaccinated children, whereas, the general incidence may be approximated as one in

⁹ YERGER, C. F. Acute toxic meningo-encephalitis of otorhinogenic origin, *Arch Otolaryngology*, 1925, 1, 198-208.

¹⁰ PINCOFFS, M. C. Benign cerebral manifestations of sinusitis, *Trans Am Climat and Clin Assoc*, 1927, xliii, 215-220.

¹¹ GRINKER, R. R. and STONE, T. T. Acute toxic encephalitis in childhood—a clinico-pathologic study of thirteen cases, *Arch Neur and Psych*, 1928, 22, 244-274.

¹² ARMSTRONG, C. Post-vaccination encephalitis, *Ann Int Med*, 1931, 1, 333-337.

300,000 It has been clearly shown that vaccine contamination cannot explain this phenomena The encephalitis or encephalomyelitis, which develops as a rule from 10 to 13 days after the vaccination, presents various striking clinical pictures which, however, would not serve to differentiate it from the other forms of non-suppurative encephalitis The mortality has varied in different countries between 17 and 70 per cent Those who survive may exhibit residual palsies for some time, but for the most part permanent sequelae have been notably rare Pathologically the disease has been shown to be an encephalo-myelitis with histological features which are not distinguishable from those seen in the similar cases following measles

The increase of these various forms of encephalitis has not failed to stimulate a search for some factor common to them all and of a nature to have been affected during these last fifteen years by some general epidemiologic influence It cannot be said that a solution has been found, but the attempts to show that these encephalitides may all be attributable to neurotropic filtrable viruses are of the greatest interest ^{13, 14, 15} The case may be summarized as follows Innumerable attempts at the isolation of a bacterial incitant have yielded mostly negative findings In a few hands such attempts have resulted in the isolation of streptococci from the brain substance of cases of encephalitis, but even the chief proponents of the streptococcus as an etiological agent have been forced to assume the existence of a filtrable form of this organism Up to the present time the evidence for bacterial causation is not convincing On the other hand there is a significant resemblance between the histologic pathology of lethargic encephalitis and that of poliomyelitis, a known virus disease, and moreover, the lesions found in these two diseases in man are similar to those found in certain known virus diseases in animals In addition to the pathologic resemblance there are certain epidemiologic features which are common to both poliomyelitis and lethargic encephalitis In particular is this true of the rarity of instances of transmission directly from one person to another On these grounds there has been a fairly general assumption that lethargic encephalitis is a virus disease

Direct search for the virus has usually been unsuccessful In a few instances a virus capable of producing an encephalitis in guinea pigs in series has been obtained from human encephalitis material The guinea pig encephalitis resembled that which can be produced by the herpes virus in these animals and did not resemble human encephalitis These findings may be explained in two ways It is known that man frequently is a carrier of the herpes virus in a latent form The virus has even been recovered from the spinal fluid of patients exhibiting no evidence of any disease attributable to it It is also known that during guinea pig transmissions of

¹³ Petro, I. M. Relation of filtrable viruses to diseases of the nervous system, Arch Neurol Psych 1932 xx, 757-777

¹⁴ Greenough, F. W. Herpes infection with especial reference to involvement of the nervous system, Medicine 1924, vii, 223-243

¹⁵ Zieve, H. T. The causation of Krasnodar, epidemic encephalitis, Arch Neurol Psych 1934, xli, 271-284

herpes virus the virus may become neurotropic and produce encephalitis. The simplest explanation then would seem to be that the very rare cases of human lethargic encephalitis from whose brain substance the herpes virus was obtained were merely carriers of this virus. There are those, however, who prefer as an explanation the more complicated assumptions, first that a human neurotropic strain of the herpes virus exists which, contrary to the human cutaneous strain, is very difficult to transmit to guinea pigs, and secondly that this neurotropic virus causes in man a type of encephalitis which is histologically quite dissimilar to that which it causes in guinea pigs. The decision as to the true part played by the herpes virus will probably have to await the next epidemic. It must be pointed out that it remains quite possible that another virus entirely may be the cause of lethargic encephalitis.

In the group of the secondary encephalitides it seems significant that the diseases which are most commonly followed by encephalitis (measles, varicella, mumps, and of late vaccinia) are also those in which a virus etiology has been either suspected or proved. In post-vaccinal encephalitis, however, in spite of numerous attempts it has only very rarely been possible to recover the virus of vaccinia from the brain substance. Proof of the virus nature of the encephalitis following these communicable diseases is still entirely lacking.

In those forms of encephalitis which are secondary to known bacterial infections such as otitis media, sinusitis, pneumonia, etc., it might seem unreasonable to invoke the possible action of viruses. However, it is known that many types of infection in man will lead to the appearance of herpetic vesicles which have been shown to contain active herpes virus. The intercurrent infection is held to have activated the latent virus which then manifests itself by the production of typical skin lesions. If the latent virus had neurotropic qualities, or if the bacterial toxins did preliminary damage to the nervous tissues then the bacterial infection in a virus carrier might be followed by a virus encephalitis.

The known virus diseases in man and those most reasonably suspected of being such are for the most part especially susceptible to epidemiological influences, and if in time to come the present interesting hypotheses as to the virus etiology of the various forms of encephalitis are shown to be well founded we may find therein an explanation of the apparent epidemic increase of all forms of encephalitis during the last fifteen years.

REVIEWS

Diseases of the Heart By WILLIAM D REID, M D, F A C P 105 pages The Graphic Press Printers, Newton, Massachusetts 1933 Price, \$ 65

This is a small, paper-bound volume of 105 pages The author has felt that students should have available some small book, more readily presenting the more important facts in regard to the symptomatology, diagnosis, prognosis and treatment of heart disease than is at present in existence, and, in his own words, the present volume is to be compared possibly to a "laboratory manual"

There is a valuable chapter on history taking in heart disease, and due stress is laid on the value of a well taken history The more important physical signs of various types of heart disease are clearly presented There is a tabulation of the information to be obtained from X-ray studies Short references only are made to the electrocardiogram and other laboratory findings in heart disease The author includes a table for immediate reference in the diagnosis of the arrhythmias Prognosis and treatment are briefly treated

The reviewer questions whether such short cuts to knowledge are of general value They are no doubt helpful to the students who can use the summary in conjunction with the personal teaching of its author For these memory will reclothe the bare bones with flesh but for others it must remain a skeleton

W S L, JR

Gastric Anacidity Its Relation to Disease By ARTHUR L BLOOMFIELD, M D, Professor of Medicine, Stanford University, San Francisco, and W SCOTT PORTLAND, M D, Instructor in Medicine, Stanford University, San Francisco The Macmillan Company, New York, 1933 Price, \$2 50

In this book the authors have presented facts about gastric anacidity which have been culled entirely from the original sources They have exposed a number of misconceptions which have been passed on from time to time in the literature It is hard to restrain oneself from the use of superlatives in an account of this volume The entire subject is covered in a stimulating, exact and highly readable manner

Misconceptions relating to the use of the term combined acidity, to the so-called hypochromic anemias, and to certain proposed etiological factors in anacidity are discussed in full The demonstration of the various concentrations of electrolytes in the gastric juice is particularly satisfying The authors have carefully sifted out the wheat from the chaff in their discussion of the various diseases with which gastric anacidity is commonly associated

There is so much new, so much sane, and so much enlightening material in the book that one has no hesitation in recommending it to all students of medicine

L M

Handbook of Pulmonary Tuberculosis By CARL V VISCHEK, M D, F A C P, with a chapter on pulmonary tuberculosis and the cardiovascular system by LOUIS L. LANGE, A B, M D vi + 199 pages 13 X 20 cm Robert F Rapp, Cambridge, N J, 1932

This small book containing 189 pages of text was written by the author shortly before he died largely from the notes of his lectures to the students of Hahnemann Medical College of Philadelphia and to nurses It is a brief systematic account of the etiology, pathogenesis, pathology, epidemiology, clinical forms, diagnosis, prognosis, and treatment The pathology of the disease is presented in a very briefly

Such a clearly written schematic account conforming for the most part to present day standardized terminology, classifications, and diagnostic and therapeutic methods should be of value especially to students, nurses and social workers

M C P

The Common Causes of Chronic Indigestion Differential Diagnosis and Treatment
By THOMAS C HUNT, B A, D M (Oxon), M R C P (Lond) William Wood and Co, Baltimore, 1933 Price, \$4 25

As its title indicates, this book deals with the more common causes of indigestion. It does not in any way pretend to be an exhaustive survey of the various etiological explanations of the multitudinous gastrointestinal pathological conditions, nor does it attempt to detail the various unusual intra-abdominal conditions which may also cause indigestion.

The subject is treated in 13 chapters which are somewhat irregularly arranged but which may be roughly divided into two main categories: organic diseases of the stomach, gall-bladder and appendix; and functional diseases of the stomach and colon. Such topics as the relationship of the cardiovascular system to indigestion, alcohol in digestion, and indigestion in old age do not come under these headings and have been treated separately. The first of these subjects is especially well handled.

In the interpretation of the symptoms of the ulcerative lesions of the stomach and of cholecystitis, the author shows himself fully cognizant of the immense amount of clinical superstition that has attached itself to these conditions. He stresses the importance of recognizing and treating the underlying factors.

In the chapter on chronic gastritis, which is full, the fundamental pathological findings do not seem to receive adequate consideration and the conclusions are at least open to criticism.

A large part of the book deals with the various functional disorders of the colon. The author's conception of the interrelationship of the psychic and organic bases of these disorders is clearly and interestingly formulated.

A minor criticism may be directed against the overuse of headings throughout the book.

This volume, as mentioned before, cannot in any way be regarded as a reference work; it offers, however, practical conceptions of the conditions discussed, obtained from a working knowledge of the subject and stated in a conservative manner.

L M

Practical Hematological Diagnosis By O H PERRY PEPPER M D, Professor of Clinical Medicine, University of Pennsylvania, and Assistant Chief of the Medical Clinic, Hospital of the University of Pennsylvania, and DAVID L FARLEY, Physician to the Pennsylvania Hospital and to the Cooper Hospital, Camden, New Jersey, and Associate in Medicine of the University of Pennsylvania. 562 pages 16.5 x 23 cm W B Saunders Company Philadelphia 1933 Price \$6 00

There seems to be a real place in medical literature for a monograph on the standard methods of modern hematology and on the purely hematological aspect not only of the diseases of the hemopoietic system but also of other diseases not primarily of the blood. The authors throughout have kept in mind their own introductory statement that hematology is primarily a handmaiden of the clinic and of practice. In Part I, which deals chiefly with hematological methods, only the methods most commonly used in the clinic are described in full but sufficient details of these are given to serve as a guide to their actual utilization. In their interpretations of the results of these methods the authors' statements are brief and specific. In disputed points references are given to the chief articles supporting the various opinions. The origin, growth and destruction of the morphological elements of the blood are presented in

a surprisingly compact description. It would perhaps have added to the interest of the book, if not to its immediate utility, if a more extended account of the work in this field had been given. In discussing the development and maturation of the red cell no mention is made of the influence exerted upon this process by the intrinsic and extrinsic gastric factors.

Part II is entitled "Hematological Diagnosis of the Diseases of the Hemopoietic System." The title is exact. The clinical aspects of these diseases and the clinical criteria, other than hematological, for their diagnosis are not included. One is confronted with pure hematology. This is so foreign to the clinician's usual way of considering the diagnosis of these conditions as to give the feeling of looking at them with one eye held closed. The limitation in scope, while artificial, is of course intentional. We gain thereby a collection of clear, full and yet succinct descriptions of the diagnostic findings in these diseases which can be derived from the examination of the blood. For quick reference or for comparative studies, this method of presentation is of distinct value.

The hematology of diseases other than those of the hemopoietic system is discussed in Part III. The diseases are arranged alphabetically which assists greatly in ready reference. The collection of data in this section will be of practical assistance to the physician in many diagnostic difficulties.

The more recent work in hematology is well represented. The references have been carefully selected, they cover the classical contributions to the development of the subject and also the latest additions to our knowledge of it.

A noteworthy feature is the ability of the authors to state briefly and fairly the gist of complicated and disputed questions. The book throughout is clearly and interestingly written. Students, laboratory workers and practising physicians will find assistance in its contents.

M C P

Further Studies on the Pharmacology of Certain Phenol Esters with Special Reference to the Relation of Chemical Constitution and Physiologic Action. The Histopathology of Some Neurotoxic Phenol Esters. By MAURICE I SMITH, Principal Pharmacologist, E W ENGL, Special Expert and E F STOHLMAN, Junior Pharmacologist, National Institute of Health, U S Public Health Service, Washington. v + 69 pages, 24 × 15 cm. United States Government Printing Office, Washington, D C, 1932. Price, 10 cents.

The wave of so-called ginger paralysis which occurred in several parts of the United States in 1930 interested the Institute of Health in the investigation of the toxicological and pharmacological nature of the phosphoric acid ester of ortho-cresol. This substance had been used as an adulterant in the extracts of ginger responsible for the poisoning.

In an effort to establish the relation of chemical constitution and physiological activity, the investigators examined twelve esters related to ortho-cresol-phosphate. The formulas and certain physical constants of the compounds are set forth in the publication.

Various types of laboratory animals were used in the examination of the compounds. The generally used avenues of drug administration were employed. Of special interest is the fact that, in cats, following the subcutaneous injection of the ortho-cresol-phosphoric acid ester of cresol practically no toxic symptoms were produced. In rabbits, however, produced a typical syndrome of bilateral and symmetrical paralysis of the distal muscles of the hind legs.

Graphs showing the rate of hydrolysis of various cresol esters are included in the publication.

The toxicity of the various esters of the cresol esters is illustrated by

microphotographs It is shown that the neurotoxic esters of phenol have a strong affinity for the anterior horn cells This action is compared with that of the virus of poliomyelitis upon the gray matter of the cord

The publication represents a fundamental investigation of pharmacological nature, interestingly written and containing material of special medical interest

J C K, JR

American and Canadian Hospitals Edited by JAMES CLARK FIFIELD, with the cooperation of the American Hospital Association 1560 pages, 21 X 27 cm Midwest Publishing Company, Minneapolis 1933 Price, \$10 00

The Editor and the American Hospital Association are to be congratulated upon the completion and publication of this valuable compilation of informative data concerning the hospitals of the United States and Canada The material is arranged geographically and alphabetically according to the system employed in the Medical Directory of the American Medical Association The hospitals in all the extra-territorial possessions of the United States and those in Newfoundland and Labrador and in the Northwest and Yukon Territories are included

The chief data given include the character of the hospital, general or special, the number of departments or services, the special facilities, the history of its construction, the number of beds, the rates, the financial status, the average number of patients, the constitution of the staff, including the house staff, the training school, the ownership of the hospital, the governing body, the name of the superintendent and of the director of the training school

Interesting historical sketches of all the associations and leagues devoted to hospital problems precede the main matter of the book, and in the Appendix information is added concerning all the religious orders in the hospital field, the important endowments or funds devoted to health purposes, the national health associations, the U S Public Health Service, the Veterans Administration, etc

Such information will be of the greatest value to all engaged in hospital work who may wish to make comparative studies of other hospitals or of problems of hospitalization It will no doubt be of fundamental aid to the work of the American Hospital Association It will be of assistance to physicians generally who may wish to know of hospital facilities at a distant point Medical students may find it of value in connection with a search for internships, and house officers may consult it in determining upon a location in which to practise There is no doubt but what the makers of all hospital equipment and supplies will use it freely It will surely become a standard reference work of great value

The appearance of the volume, the binding and typography are a credit to the publishers

M C P

COLLEGE NEWS NOTES

Dr Walter L Bierring (Fellow and Regent of the American College of Physicians) was elected President-Elect of the American Medical Association at its last annual meeting in Milwaukee during June

Dr Bierring has had a significant career in medical organization. He has been President of the Iowa State Board of Medical Examiners, President of the National Board of Medical Examiners, President of his County and State Medical Societies, President of the Alpha Omega Alpha, honorary medical fraternity, and is President of the Iowa State Board of Health. He has been a Fellow of the American College of Physicians since 1928, and a member of its Board of Regents since 1930.

Dr John H Musser (Fellow and Regent), New Orleans, was elected Vice-President. Dr Nathan B Van Etten (Fellow), New York City, was elected Vice-Speaker. Dr James S McLester (Fellow and Regent), Birmingham, Ala., was appointed a member of the Committee on Medical Education and Hospitals, and Dr J E Paulhn (Fellow), Atlanta, Ga., was appointed a member on the Council of Scientific Assembly.

Dr Louis Faugeres Bishop, Sr (Fellow), New York, N Y., was elected President of the American Therapeutic Society for the years 1933-1934, at the annual meeting of that Society held in Milwaukee, Wis., June 9 to 10, 1933.

Dr Edward B Krumbhaar (Fellow), and Dr William D Stroud (Fellow and Treasurer), both of Philadelphia, were elected President and Vice-President, respectively, of the Philadelphia Heart Association at its annual meeting in April.

Dr Paul Dudley White (Fellow), Instructor in Medicine at Harvard University Medical School, was the speaker.

The May issue of *Radiology* was dedicated to Dr Albert Soiland (Fellow), Los Angeles, Calif., "in acknowledgment of his achievements in radiology and in recognition of his sixtieth birthday." Dr Soiland was the founder of the American College of Radiology, and is at present a member of the House of Delegates of the American Medical Association.

Under the Presidency of Dr Adolph Sachs (Fellow), of Omaha, the Nebraska State Medical Association held its Sixty-fifth Annual Meeting in Omaha, May 23 to 25, 1933.

Dr Charles A Elliott (Fellow), Professor of Internal Medicine at Northwestern University Medical School, Chicago, Dr H L Bockus (Fellow), Professor of Gastro-Enterology, Graduate School of Medicine of the University of Pennsylvania, Philadelphia, and Dr Walter Clarke (Fellow), Director of Medical Activities, American Social Hygiene Association, New York City, were guests of honor and delivered addresses in their respective fields.

The Mississippi Medical Society conducted a postgraduate medical institute from June 6 to 9, 1933, inclusive.

Dr George Heeren (Fellow), Professor of Clinical Medicine at the University of Maryland, Editor of the *American Journal of Syphilis*, Associate Editor of *Journal of the American Medical Association*, and Physician to the Johns Sealy Hospital of Baltimore, and Dr Joseph C Bloomberg of Baltimore, Md., conducted lectures.

At the tenth anniversary meeting of the American Society of Stomatologists, in New York City on April 27, 1933, the CHOMPRET PRIZE was awarded to Dr Oliver T Osborne (Fellow), Emeritus Professor of Therapeutics at Yale University School of Medicine, for his "Meritorious contributions to the science of stomatology and for his untiring labors to bring dentistry and medicine to a plane of better understanding and appreciation of their common problems for the good of mankind"

Dr Anthony Bassler (Fellow), New York City, made the presentation address, as follows

"The American Society of Stomatologists, together with the International Academy of Stomatology, has therefore deemed it an honor to commemorate the work of this great pioneer in stomatology (Dr Joseph Chompret) by establishing the CHOMPRET PRIZE, symbolized by a gold medal to be awarded every second year to the deserving person who has made the most outstanding contribution to the progress of stomatology either in the realm of science or in the professional advancement of the stomatologic specialty This medal will be awarded at the recommendation of the CHOMPRET PRIZE COMMITTEE of the International Academy of Stomatology and the American Society of Stomatologists"

Dr James J Waring (Fellow) has been appointed Professor of Medicine of the University of Colorado During the past year he was elected Vice-President of the Western Branch of the American Public Health Association, and a Director of the National Tuberculosis Association and member of its Executive Committee

Dr James L McCartney (Fellow), Psychiatrist and Director of Classification, New York State Department of Correction, Elmira Reformatory, has been awarded a grant of \$1,000 00 by the Thomas W Salmon Memorial Committee of the New York Academy of Medicine for investigation on the classification of prisoners and the drawing up of a handbook on classification for use in prisons

Dr McCartney for the past two years has been Director of the Classification Clinic at Elmira Reformatory, and is Secretary of the Medical Section of the American Prison Association, as well as a member of the Committee on Case Work and Treatment of the American Prison Association, which is attempting to standardize the scientific examination and care of prisoners in this country

A report of this Committee is to be given at the forthcoming congress of the association, which is to be held in Atlantic City the second week of October

Dr Solomon Solis-Cohen (Fellow), Philadelphia, Pa, received the honorary degree of Doctor of Science at the recent 108th annual commencement at Jefferson Medical College of Philadelphia

Dr Solis-Cohen was a graduate of the Class of 1883 of this institution and is Emeritus Professor of Clinical Medicine

Dr Albert E Russell (Fellow), Washington, D C, has been appointed Chief Surgeon of the U S Bureau of Mines

Dr Russell addressed the Toledo (Ohio) Academy of Medicine on May 5, 1933, on the subject of occupation and respiratory diseases

Dr Samuel E Thompson (Fellow), Kerrville, Tex, was elected President-Elect of the State Medical Association of Texas at its annual meeting in May

Dr G L Pinney (Fellow), Hastings, Nebr, was recently elected Vice-President of the Nebraska State Medical Association



DR WILLIAM BLAIR STEWART

OBITUARIES

DR WILLIAM BLAIR STEWART

Dr William Blair Stewart was of Scotch-Irish descent, son of a physician and grandson of a physician. He was born March 6, 1867, at Middle Spring, Pa, in the Cumberland Valley. Soon after his birth, his family removed to New Brighton, in the western part of the State, where they remained with his maternal grandfather for two years. They removed to Newburg, a hamlet near Middle Spring, where his father practised medicine until 1873. The family then moved into the adjoining town of Newville, which remained his home for many years, and to which he loved to return, in later life, twice a year to renew old acquaintances and to fish in the creek.

Dr Stewart entered Dickinson College, Carlisle, Pa, receiving the Ph B degree in 1887 and the M A degree subsequently. His enduring loyalty to his Alma Mater was rewarded forty-five years later by his election to the Vice-Presidency of the Alumni Association of that institution. In 1890 he was graduated with highest honors from the Medico-Chirurgical College of Philadelphia, in which he also served as Instructor in Therapeutics.

After spending the summer of 1890 in Atlantic City as assistant to Dr Boardman Reed, and seven months on Fairmount Avenue in Philadelphia, he removed to Bryn Mawr, where he practised medicine for three years. In August 1894, he moved to Atlantic City, N J, as a permanent resident, assisting Dr Reed at first and later taking over his property at the corner of North Carolina and Pacific Avenues when Dr Reed retired in 1898. It was here he brought his bride, Florence Elizabeth Giffin, in 1897, here were born his children, Walter in 1898 and Sloan in 1901—both physicians at present—and here he died on July 11, 1933, at the age of sixty-six.

The three great interests in his life were family, society and medicine, intermingling all of which was a pervasive love of and faith in humanity. He made friends readily, but enemies rarely. Friends made were friends retained. His loyalties were strong. He was friend of the child, the elevator boy, the delivery man. There was always some witticism on the end of his tongue, or some bit of humor "up his sleeve", an unusual ability in ventriloquism often baffled friends and charmed animals. His three grandchildren were his greatest source of pleasure in his latter years. Seldom was there a day when he would miss the noon visit with them.

As evidence of his civic interest, he had been President of the Atlantic City Board of Trade, Director of the Chamber of Commerce, member of the Board of Education, President of the Board of Trustees of the First Presbyterian Church and a Director of the Young Men's Christian Association. One may best quote from an editorial in the *Atlantic City Press*: "Dr W Blair Stewart, who died this week, should be long remembered for his upstanding citizenship no less than his high professional rating and worth. Always a conservative, of sound and practical judgment, he was ever to be found working diligently for projects which meant worthwhile

progress for Atlantic City, against projects which smelled of malodorous politics or other civically-destructive influences " His political faith was always Republican He was a thirty-second degree Mason and a Knights Templar In the Atlantic City Rotary Club he had a perfect attendance record for the past eight years, and maintained a keen interest in all the activities of the Club

He was the author of a textbook on medicine, "A Synopsis of the Practice of Medicine," in his earlier years, and he frequently contributed articles to various medical journals His medical name first came into local and national prominence in his successful efforts in the late nineties to eradicate the serious menace of typhoid fever from Atlantic City, a menace that has never returned He was an ex-President of the Atlantic County Medical Society, and had always taken an active rôle in the New Jersey State Medical Society For many years he was a Surgeon to the Atlantic City Hospital, but later, feeling an increasing fondness for Internal Medicine, he gave up major surgery and worked solely as an internist He was a former Vice-President of the American Medical Association and one of the early (1916) Fellows of the American College of Physicians For several years, he had been Chairman of its Board of Governors and a member of the Board of Regents

Although in the last years of his life he observed the insidious development of coronary disease and myocarditis, especially in the final year, he dreaded the prospects of a life of invalidism, but insisted rather in remaining "in harness" until the end, which came suddenly, as he would have had it

WALTER B STEWART, M D

DR THOMAS JEFFERSON McKINNEY

Dr Thomas Jefferson McKinney (Associate), Champaign, Illinois, died May 27, 1933, in the Kenilworth (Ill) Sanitarium, aged, 73 years

Dr McKinney was born at Muncie, Indiana He attended the Illinois State Normal University and entered the Medical College of Indiana, from which he received his degree of Doctor of Medicine in 1883 After a few years of practice, he secured the degree of Doctor of Medicine from the Northwestern University Medical School in 1898 He pursued postgraduate training at the Chicago Post Graduate Medical School, the Chicago Polyclinic and the New York Post Graduate Medical School He was a member and former President of the Champaign County Medical Society, a member of the Illinois State Medical Society, and a member of the American Medical Association He was a teacher in mental and nervous diseases to nurses and President of the Staff of the Burnham City Hospital He had been an Associate of the American College of Physicians since 1926.

NATIONAL POISON IVY ANTIGENS



The treatment of poison ivy (rhus dermatitis) was purely symptomatic and most unsatisfactory until the active antigen for specific treatment was produced

Relief in a few hours and a complete cure in a few days may now be expected by using the specific Rhus Tox Antigen for poison ivy, Rhus Venenata Antigen for poison oak

These Antigens are prepared under U S Government License No. 102 and are accepted by The Council on Pharmacy and Chemistry of The American Medical Association

Reprint from original articles published in The Journal of The American Medical Association, The Medical Journal and Record, Archives of Dermatology gives full information and will be mailed on request The reports of Williams and MacGregor of The New York Skin and Cancer Hospital, Brings of Atlanta and Strickler formerly of Temple and Philadelphia General Hospitals may be accepted without question

The Antigens retain their potency for at least three years, furnished in packages containing four 1 cc Ampoule-Vials Physician's price \$3 50

THE NATIONAL DRUG COMPANY
PHILADELPHIA
U.S.A.



Mail Literature on Poison Ivy per Annals of Internal Medicine

Name

Address

Date

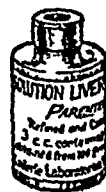
Please Mention this Journal when writing to Advertisers

Economy in Liver Therapy

DOCTOR William P. Murphy of the Peter Bent Brigham Hospital, Boston, Mass., recommends (Journal A. M. A., March 26, 1932), the use of intramuscular injections of material derived from 100 grams of liver as an economical and satisfactory method of treating pernicious anemia.

He states:

"Finally, mention may again be made of the economy possible through the use of parenteral extract as compared with the expense of either liver or liver extract administered orally."



One Half
Actual Size

Solution Liver Extract Lederle

is a concentrated product. It is marketed in packages of three vials, each vial containing in three cubic centimeters the material obtained from 100 grams of liver. It is thus convenient for carrying out the effective dosage as recommended by Murphy.



Full information upon request

LEDERLE LABORATORIES INC., NEW YORK
511 FIFTH AVENUE

ARTERIOSCLEROSIS

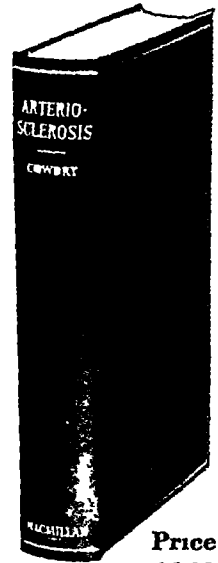
A SURVEY OF THE PROBLEM

Edited by

E. V. COWDRY

*Washington University,
St Louis*

A Publication of the
**JOSIAH MACY, JR
FOUNDATION**



Price
\$5 00

With the publication of this distinguished volume, the doubts and confusion of years have been set aside

International in scope, searching in its treatment, every aspect of the subject has been covered

Contributors

N. ANITSCHKOW
LUDWIG ASCHOFF
E. T. BELL
DANIEL BLAIN
CRIGHTON BRAMWELL
STANLEY COBB
ALFRED E COHN
E. V. COWDRY
HERBERT FOX
JONAS S FRIEDENWALD
HOWARD T KARSNER
FRITZ LANGE
ESMOND R. LONG
W G MACCALLUM
GEORGE R MINOT
WILLIAM OPHULS
A POLICARD
PERCY STOCKS
EDGAR SYDENSTRICKER
SOMA WEISS
H GIDEON WELLS
GEORGE DEE WILLIAMS
JOHN H WICKOFF

Comment

"It can be said with confidence that this volume constitutes the most complete, the most authoritative, and the most illuminating and outstanding contribution to the study of Arteriosclerosis yet made. Student, investigator, pathologist, physician at large—all can read it with profit. Without doubt it will remain an outstanding reference work for some time to come"

—*Jl of Laboratory and Clinical Medicine*

Contents

Introduction	XI Chemistry of Arteriosclerosis
I Development of our Knowledge of Arteriosclerosis	XII Acute and Chronic Infections as Etiological Factors
II Structure and Physiology of the Blood Vessels	XIII Retinal Arteriosclerosis
III Physical Properties of Arteries in Health and Disease	XIV Arteriosclerosis of the Brain and Spinal Cord
IV Mineral Constituent of Blood Vessels as Determined by the Technique of Coordination	XV Coronary Arteriosclerosis
V Statistical Study of Arteriosclerosis	XVI Sclerosis of the Pulmonary Arteries
VI Arteriosclerosis in Lower Mammals and Birds	XVII Arteriosclerosis of the Abdominal Viscera and Extremities
VII Race and Climate as Possible Factors	XVIII Hypertension in Relation to Arteriosclerosis
VIII Nutrition in Relation to Arteriosclerosis	XIX Hereditary Aspects of Arterial Hypertension in Relation to Arteriosclerosis
IX Pathogenesis of Arteriosclerosis	XX Treatment of Arteriosclerosis
X Experimental Arteriosclerosis in Animals	XXI Summary

THE MACMILLAN COMPANY

Publishers

New York

Boston

Chicago

Dallas

San Francisco

Atlanta

The Macmillan Co
60 Fifth Ave., New York

Please send me one copy of

Cowdry's **ARTERIOSCLEROSIS** Price \$5 00
(Check herewith or charge my account)

Name _____

Address _____

City—State _____

Bromural

Alphabromisovalerylcarbamide

Council Accepted

AS A ROUTINE SEDATIVE

in general nervous disturbances prescribe one tablet (5 grains) several times a day. As a mild and prompt hypnotic the dose is 2 to 3 tablets upon retiring or during the night. Bromural is not a barbiturate nor a bromide.

5 grain tablets and as a powder.

Samples and literature upon request

Bilhuber-Knoll Corp.,

154 Ogden Avenue, JERSEY CITY, N. J.



*Definite dosage
Ease of administration
Sensible economy*



Each pill contains 0.1 gram (1 1/2 grains) of physiologically tested digitalis leaves. The leaves are carefully dried, thus giving reassurance of their activity.

Each pill represents 15 minims of the U. S. P. tincture and permits of more accurate dosage than the tincture, which may vary in size.

The pills contain digitalis in its complete form and not any separated or extracted part of it, thus giving the most reliable copy of the standard drug.

Please send for size pills and literature sent free upon request

DAWSON, ROSE & CO., Ltd

100 South Market Street, BOSTON, MASS.

Devitt's Camp, Inc.

ALLENWOOD
PENNSYLVANIA

(Tuberculosis)

*On beautiful White Deer Mountain, 20 miles southeast
of Williamsport, Pa*

All modern methods of treatment, including heliotherapy, artificial pneumothorax, phrenic exaeresis, Jacobaeus operation, and thoracoplasty

Not operated for profit Moderate rates Modern buildings

Patients given individual attention by experienced physicians and specially trained registered nurses

The following physicians will be glad to examine patients for admittance to Camp

J M ANDERS, M D, Philadelphia, Pa
ISABEL M BALPH, M D, Philadelphia, Pa
E J G BEARDSLEY, M D, Philadelphia, Pa
WARD BRINTON, M D, Philadelphia, Pa
F W J BURGE, M D, Philadelphia, Pa
DAVID A COOPER, M D
DONALD R FERGUSON, M D, Philadelphia, Pa
JOHN B FLICK, M D, Philadelphia, Pa
JOHN A KOLMER, M D, Philadelphia, Pa
W ESTELL LEE, M D, Philadelphia, Pa
A C MORGAN, M D, Philadelphia, Pa
ARTHUR W PHILLIPS, M D
GEO MORRIS PIERSOL, M D, Philadelphia, Pa
EDWARD R SNADER, Jr, M D, Philadelphia, Pa
MERVYN R TAYLOR, M D, Philadelphia, Pa
THOS J VISCHER, M D, Philadelphia, Pa
A S KECH, M D, Altoona, Pa
CHARLES C HABLSTON, M D, Baltimore, Md
CHARLES S AITKEN, M D, Brookline, Pa
J C ATWELL, M D, Butler, Pa
F DECARIO, M D, Bradford, Pa
J W WOOD, M D, Chester, Pa

JOHN E FRETZ, M D, Easton, Pa
RICHARD R DALRYMPLE, M D, Erie, Pa
JESSE L LENKER, M D, Harrisburg, Pa
H B ANDERSON, M D, Johnstown, Pa
JOHN H ESBENSHADE, M D, Lancaster, Pa
E J WERLE, M D, Meadville, Pa
CHARLES G CRANE, M D, Newark, N J
W A WOMER, M D, New Castle, Pa
EDWARD S MCSWEENEY, M D, New York City
M THERESA SCANLAN, M D, New York City
STANLEY L WANG, M D, New York City
W R GLENNEY, M D, Pottsville, Pa
R R JONES, M D, Pittsburgh, Pa
C L PALMER, M D, Pittsburgh, Pa
A H COLWELL, M D, Pittsburgh, Pa
HOWARD U MILLER, M D, Reading, Pa
A E DAVIS, M D, Scranton, Pa
H D WILLIAMS, M D, Trenton, N J
B M ALLEN, M D, Wilmington, Del
JOHN MINOR, M D, Washington, D C
J W PEABODY, M D, Washington, D C
H R SCHREIBER, M D, Washington, D C
E W BIXBY, M D, Wilkes Barre, Pa
HARRY M READ, M D, York, Pa

BOOKLET

ROSS K CHILDERHOSE, M D
JOHN S PACKARD, M D
Associate Physicians

WILLIAM DEVITT, M D
*Superintendent and
Physician in Charge*

New LEA & FEBIGER Books

NEW WORK

JUST READY

DIETETICS FOR THE CLINICIAN

By MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P.
Associate in Medicine at the New York Post-Graduate Medical School, Columbia University, New York

IN COLLABORATION WITH
RUTH LOTHROP GALLUP
Dietitian

WITH A FOREWORD BY
HERMAN O. MOSENTHAL, A.B., M.D.
Director of Medicine at the New York Post-Graduate Medical School, Columbia University, New York
Octavo, 666 pages Cloth, \$6.50, net

This work presents dietary management in readily understandable form. Four hundred pages are devoted to the dietetic indications of over one hundred common diseases, furnishing sample menus for three days in each case. It is of real practical value not only to the general practitioner but to the specialist as well. The surgeon, pediatrician, dentist, otolaryngologist, endocrinologist, urologist and the specialists in tuberculosis, allergy and diabetes will find here material of great practical value prepared in collaboration with experts in each field.

NEW (2nd) EDITION

JUST READY

CALCIUM METABOLISM AND CALCIUM THERAPY

By ABRAHAM CANTAROW, M.D.
Professor of Medicine, Jefferson Medical College, in Charge of Laboratory of Biochemistry, Jefferson Hospital, Assistant Physician, Philadelphia General Hospital

WITH A FOREWORD BY
HOBART AMORY HARE, B.Sc., M.D., LL.D.
Professor of Therapeutic Materia Medica and Diagnosis in the Jefferson Medical College, Philadelphia
12mo, 252 pages, illustrated, limp binding, \$2.50, net

The discovery of the antirachitic factor and the parathyroid hormone resulted in the rapid development in this field reflected in the accumulation of a voluminous literature. Ten years ago hardly any of the now well-established principles could have been presented, even if attempted. This work has kept pace with the rapidly accumulating knowledge and should be known to everyone on a rational basis.

NEW BOOK

JUST READY

A TEXT-BOOK OF NEUROPATHOLOGY

By ARTHUR WEIL, M.D.
Professor of Neurology, Northwestern University Medical School, Chicago, Illinois
12mo, 500 pages, illustrated with 260 engravings Cloth, \$5.00, net
This text-book covers every recent advance and summarizes the present state of the literature. It gives a full understanding of the pathology of the nervous system and is a reliable guide in all clinical work. The clinical features of the various diseases are fully explained.

LEA & FEBIGER

600 Washington Square
PHILADELPHIA

<input type="checkbox"/> By Express \$6.50	[<input type="checkbox"/> Well \$5.00
<input type="checkbox"/> Cash 2.50		<input type="checkbox"/> New Catalogue
Address		

In Every Physician's Bag . . .

The many emergencies in which it is urgently needed—traumatic shock, apparent death, anaphylaxis, serum reactions, and asthmatic paroxysms—suggest the wisdom of always keeping a supply of Adrenalin* in the emergency bag.

Many clinicians with wide experience in immunization work inject Adrenalin preceding or with the injection of biologicals or other substances containing foreign proteins, in cases where the patient is suspected of being subject to allergic reaction. This simple precautionary measure may prevent allergic reaction and may be the means of preventing a serious or even fatal protein shock.

A supply of Adrenalin ampoules in your office and in your emergency bag not only provides a means of preventing allergic reactions, but may enable you to administer life-saving medication in an emergency.

Adrenalin Chloride Solution 1:1000 is available in one-ounce bottles and in boxes of one dozen and one hundred 1-cc. ampoules (Ampoule No. 88).

*The Parke-Davis brand of Epinephrine, U S P.

PARKE, DAVIS & COMPANY

*The World's Largest Makers of
Pharmaceutical and Biological Products*



Please Mention this Journal when writing to Advertisers

BETTER ASSAY CONTROL » » » BETTER CLINICAL CONTROL



TWO EXCELLENT
REASONS WHY
PHYSICIANS USE
AND PRESCRIBE

WYETH'S CAPSULES DIGITALIS LEAF (DEFATTED)

(EACH CAPSULE CONTAINS ONE CAT
UNIT—15 MINIMS U.S.P. TINCTURE)

1. Better Assay Control

Every batch of Wyeth's Digitalis Leaves is submitted to TWO methods of standardization—the one-hour U.S.P. frog method and the cat unit method of Hatcher and Brody.

In this way possible variation in biological assay is reduced to a minimum and every batch is brought to greater uniformity.

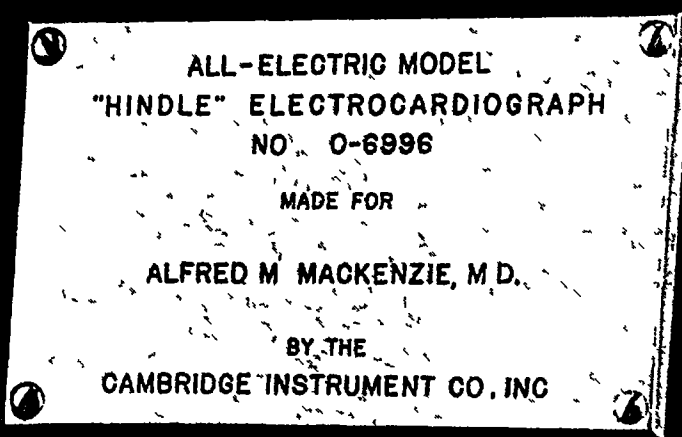
2. Better Clinical Control

Each capsule contains a definite and unvarying amount of carefully standardized drug. No uncertain dropper or complicated measuring device is needed to gauge dosage—the patient is protected against possibility of error. Supplied in vials of 36 and 100 attractive green capsules in suitable containers for dispensing.

Control the integrity of your prescriptions
by specifying Wyeth's pharmaceuticals

JOHN WYETH & BROTHER, INC.
PHILADELPHIA, PA. AND WALKERVILLE, ONT.





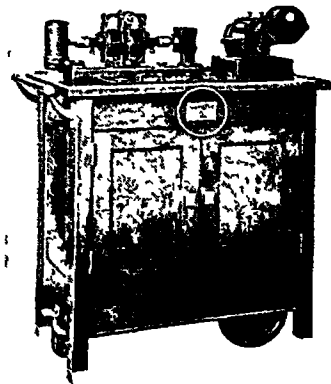
THIS NAMEPLATE

EVERY "Hindle" Electrocardiograph has a nameplate upon which is engraved not only the identification of the instrument but the name of the doctor or hospital for whom it is made. We are proud to link our name with the names of many of the foremost American Cardiologists and institutions. The Cambridge Instrument Company with due appreciation of this honor bends every effort to produce the finest, most accurate and dependable electrocardiograph for the service of the medical profession. The science of electrocardiography has been developed in the United States almost entirely upon the "Hindle" Electrocardiograph.

**CAMBRIDGE
INSTRUMENT CO. INC.**

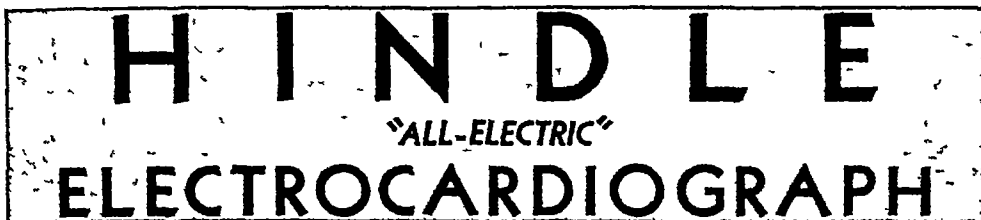
"Pioneer Manufacturers of the Electrocardiograph"

3732 Grand Central Terminal
New York City



The New "All-Electric" models are made in stationary, mobile and portable types for hospitals, clinics and private offices.

Send for Literature





The physician's
REPUTATION
is gaged by his ability
to treat disease . . .

SUCCESSFUL treatment demands cooperation by chemist and pharmacist, and any shortcomings on their part may impair the therapeutic results.

Chemical science now and again succeeds in bringing to light some valuable addition to the materia medica. Luminal, among these, has proved an important contribution to the treatment of epilepsy, and nothing has been devised to supplant it in this disease. Its scope has greatly widened and now includes a host of other disorders.

Consequently, in prescribing Luminal the physician bases his specification upon the cumulative observation of thousands of clinicians. He is also assured of uniform quality founded on years of manufacture under the supervision of the same expert chemists.

LUMINAL

U. S. PAT. 1,172,861
 ESTER OF PHENOBARBITAL



WINTHROP CHEMICAL COMPANY, Inc., New York, N. Y.

What the "DEAN of AMERICAN MEDICINE" says . . .

DR. WM H WELCH, of Johns Hopkins University, considered by a host of medical authorities "The Dean of American Medicine,"* recently stated at the New York Academy of Medicine

"Too great economy, as far as health is concerned, because of the current depression, is particularly dangerous to the welfare of growing children. Undernourishment of children, for example, is not likely to show itself immediately, but is bound to show itself later when it is probably too late to remedy it. The ground lost by undernourishment in childhood may never be regained."

Physicians everywhere are being told by patients, that because of reduced incomes their family budgets are being slashed. This means reduced diets. It is well to point out in such instances that, in spite of reduced family budgets, the health of growing children must be safeguarded. Often a child needs only the addition of a balanced, prophylactic compound—such as Maltine With Cod



Liver Oil—to render an otherwise insufficient diet completely adequate

In conditions due to deficiency of Vitamins A, B (b_1), G (b_2), or D, Maltine With Cod Liver Oil will prove its worth. It is composed of 70% Maltine, a concentrated extract of the nourishing elements of malted barley, wheat and oats—rich in Vitamins B and G—and 30% pure vitamin-tested cod liver oil of high potency in Vitamins A and D. Taken with orange or tomato juice, Vitamin C is added.

Maltine With Cod Liver Oil is biologically standardized and guaranteed to contain four vitamins, A, B (b_1), G (b_2), and D. Biological report on request. The Maltine Company, Est 1875, 30 Vesey Street, New York, N Y.

Maltine

WITH COD
LIVER OIL



* Taken from Medical Journal and Record

Calcium-Phosphorus Deficiencies IN DENTAL CARIES

THE *Annual Review of Biochemistry*, 1932, cites as among the more important developments in biochemistry for 1931 studies attesting the clinical value of vitamin D in arresting dental caries.¹

"Clinical trials of the value of vitamin D in arresting dental decay in children have been strikingly successful," the report states further.

Many theories have been put forth concerning the etiology of dental caries, but since it is recognized that the composition of teeth is largely calcium and phosphorus and that the tooth has a circulatory system, it is logical to suppose that the calcifying factor, vitamin D, is essential for sound tooth structure.

Vitamin D for Arrest of Caries

Recent studies point especially to the efficacy of viosterol in dental prophylaxis. A 2-year study of 800 English children receiving various dietary additions showed irradiated ergosterol to be of striking value in arresting dental caries, the rate of spread of caries being only one-third that of the control group.

Write for new literature, "The Dental Value of Vitamin D in Pregnancy and Lactation."

Price,² Boyd and Drain,⁴ Davis,⁵ and the Toveruds⁶ are among the numerous other authorities whose clinical studies reveal that vitamin D improves tooth structure or inhibits decay.

Vitamin D for Adults

McCollum, referring to studies by himself and associates, states, "Decay, we believe, is the result, in most instances, of a diet unsatisfactory in respect to its calcium, phosphorus and vitamin D content."

Speaking of Mellanby's work, he continues, "Her results harmonize with our interpretation that a dietary regimen which tends to maintain the phosphorus and calcium of the blood at a high level tends to render the individual caries-immune. I believe no one alert to existing knowledge would hesitate now to state unqualifiedly that the pregnant and nursing mothers of today are getting too little vitamin D. If our studies and those of Mrs. Mellanby are as sound as we believe they are, they will afford evidence that in temperate regions people of all ages should take some source of vitamin D."

MEAD'S CEREAL

ENRICHED WITH MINERAL AND VITAMIN CONTAINING FOODS

SUPPLIES Calcium and Phosphorus

This tasty food contains 6 times more calcium than fluid milk, formerly one of the best sources of this mineral. Two ounces of Mead's Cereal alone supplies the adult's daily minimum requirement of 0.45 Gm. Ca. In addition, Mead's cereal is richer in phosphorus than the principal foodstuffs. For sale at drug stores, in 1- and 4-lb. packages.

* * * Photographs on request

MEAD'S VIOSTEROL

in Oil 250 D

UTILIZES Calcium and Phosphorus

Mead's Viosterol maintains serum calcium and phosphorus in proper ratio and enables the body to store these minerals in bones and teeth. It is the most potent type of vitamin D product commercially available. It is offered as a dental prophylactic of utmost purity and uniform potency. Packed in brown bottles and light-proof cartons.

MEAD JOHNSON & CO., Evansville, Ind., Pioneers in Vitamin Research

"The Mead-Johnson Vitamin Research Department has been studying the relationship between the diet and the health of the body for many years. It is the result of this research that we have developed the most effective and reliable method of supplying the body with the vitamins it needs for good health."

For more information, write to Mead-Johnson Vitamin Research Department, Evansville, Ind.

ANNALS OF INTERNAL MEDICINE

VOLUME 7

SEPTEMBER, 1933

NUMBER 3

THE INTERNIST AS HIS OWN PSYCHIATRIST*

By ALFRED STENGEI, M D , M A C P , *Philadelphia, Pennsylvania*

THE TERM psychiatrist as used in the title and the following discussion is intended to indicate not only the physician's relation to psychiatry proper but also to psycho-neurology and the whole range of functional diseases and all of the disorders attributable to disturbances of the sympathetic and parasympathetic systems. All of these fields of study are so interrelated that at least from the internist's standpoint wide separation is undesirable and in the absence of a comprehensive designation I have chosen the term psychiatrist to indicate the physician's relation to all nervous and mental backgrounds of disease as well as the psycho-neurologic consequences of diseases falling under his care.

The reciprocal relations of somatic disease or disease manifestations and psycho-neurologic conditions are so important that it is unnecessary to offer any apology for bringing them to the attention of a College of Physicians and no defense is needed for saying that clinicians commonly approach their study of disease with too little appreciation of the psychiatric antecedents or consequences. With no less frequency, however, psychiatrists expend all their energies on the psychic or neurologic aspects of disease lacking either the training in clinical medicine or a proper appreciation of its significant bearing on psychiatric problems.

A closer cooperation of the two groups is essential to sound clinical medicine and more serious efforts to teach medical students the psychiatric responsibilities of the clinician would greatly widen his understanding of human disease. So far as this teaching is concerned I submit that the proper place for it is in the wards of the general hospital and that it is an important duty of clinical teachers to emphasize this aspect of general medicine.

As the limitations of this discussion will prevent enlargement on all of its aspects I shall content myself with the single statement regarding treatment, that the physician who underrates or ignores the psychic factors in disease, even the grossly organic diseases, loses an opportunity for effective treatment that would distinguish the successful from the unsuccessful medi-

* Read at the Montreal Meeting of the American College of Physicians, February 9, 1933

cal practitioner Internists with broad experience in the practice of general medicine need not be told that varied conditions affecting the personal or domestic life of the patient have great significance in the etiology and in the manifestations of disease, but they are on the other hand often unduly disturbed by psychiatric episodes which are but a part of the whole clinical picture

Internal medicine, it must be confessed, still labors too greatly under the domination of the school of pathological anatomy However greatly medicine was indebted to Virchow and the other noted morphologists for their systematizing of disease and establishing clear understandings of the anatomical basis of many conditions, it must be recognized that time has brought about great advances in entirely new directions The contributions of chemistry and physiology in particular have established viewpoints of the dynamics of many diseases that render the older static or morphological conceptions largely lifeless The complicated and widely distributed manifestations and effects of certain general diseases and infections push into the background of relative unimportance the limited pathological lesions that may perhaps with justification be regarded as representing the primary foci or seats of onset A real knowledge of disease requires an understanding of the complexities of the mechanisms of adjustment that follow an initial fault and not infrequently the struggle for compensations occasions new clinical pictures that show little evidence of relation to the primary lesion, which thus becomes dwarfed by contrast The search for organic lesions, important as it undoubtedly was and still remains, may therefore prove a fruitless method of advancing knowledge of disease It served its purpose more largely before etiology, chemistry, and clinical physiology had reached their present-day stages of development, but unfortunately the impress on medicine was so great that the physician of today is still obsessed with the notion that the discovery of an anatomical lesion and the naming of a disease is the end of his diagnostic labors His whole attitude toward disease and the directions of his therapeutic efforts are dominated by this point of view, and he stands aghast at the amazing fact that forms of unorthodox treatment which seemingly adapted to the case, under his anatomical conception, sometimes accomplish practical results

To be a little more specific let us consider one illustration Fatigue is perhaps the most frequent and most important single cause of disease, and under its influence one local manifestation after another, often functional in character, of organic in nature, may develop or there may be a simultaneous development of several "diseases" Each of these may perhaps be skillfully treated as purely local conditions but when the source or trouble is unrecognized, successful local treatment may be followed by new outbreaks of disease and it is a sad enough to have known Weyl Mitchell or are to have been a contemporary will not need to be told that his recognition of the importance of fatigue and his practical system for its correction have been a great boon to many a patient It is deeply to be regretted that his method

were fundamentally adapted to restore health as well as to prevent recurrences of the same sort or of other types of disease

Nowhere in the domain of internal medicine are the confused relations between causes, results and compensations so important as in the association of visceral or bodily diseases and neuro-psychiatric conditions. Familiar as internists are with organic diseases and despite their daily contact with the beginnings and lesser grades of psychiatric disorders, it seems a regrettable fact that they have too commonly little appreciation of the significance of such conditions and, when more marked psycho-neurotic manifestations occur, fall into a panic and look to the psychiatrist for help. This condition of things is not wanting in explanation. Psychology and psychiatry have advanced very rapidly and have grown greatly in importance. Unfortunately a veritable welter of terminology and a multiplicity of "systems" have created the impression that the field is so difficult that none but the pure specialist needs aspire even to a modest understanding. Without invading this dangerous controversial territory too deeply we may at least suspect that when groups within a certain field speak in varied vocabularies and are scornful of one another, fact and fable must be considerably commingled.

It is entirely possible for the clinician to cultivate a psychiatric point of view and unless he does so many of his greatest problems and opportunities will escape him. A properly cultivated appreciation of the fact that the causation of many conditions seemingly due to organic visceral disease may be found in neurologic or psychic backgrounds or in environmental conditions is as necessary to the trained internist as is a knowledge of the biochemical or physiologic changes which accompany certain diseases and more directly cause wide-spread results than the original anatomical defect. It is part of the clinician's routine duty to recognize and determine by appropriate tests these latter factors in disease without calling upon chemists or physiologists to point them out. In the same sense it is essential to his efficiency that his apprehensions should be alive to the neuro-psychological relationships. A broader and better cultivation of this whole field on the part of both the internist and the psychiatrist is eminently desirable, and though I have just referred especially to the internist as falling short of his responsibilities may I not add with equal frankness that if experience in clinical medicine and a knowledge of the natural history of disease on the part of the psychiatrist were wider and sounder, considerable parts of his systems and credulities might be eliminated. Without enlarging upon the psychic aspects of the etiology of disease which have been so greatly emphasized in recent years, often as if they represented new discoveries, it may suffice to say that much recent literature presents quite old and good wine in new bottles. The psychogenic nature of symptoms, functional disorders or even of organic disease was not unrecognized by sound clinicians of the past even as far back as Sydenham.

A distinguished physician of the psychiatric type, but a sound clinician

besides, presented before this College a proposal that the psychiatrist of a hospital should accompany the physician in daily rounds and while he very properly indicated the advantage of this to the clinician and the patient I would beg to add that the wider horizon of the psychiatrist resulting from such an arrangement would be not the least of its benefits. One of the major diseases of medicine at the present day is the fulminant character of specialism. All admit it, yet few seek earnestly to correct it. That a more prolonged exposure to intimate contact with disease in the capacity of a general physician is a desirable foundation for specialism is as true of the neuro-psychiatrist as it is of any other specialist, and it may be added that closer association of those whose responsibilities lie in the broad field of general medicine with such specialists as the psychiatrist cannot but prove helpful to both.

However the result is accomplished, my purpose here is to emphasize the fact that a very keen psychiatric point of view is essential to the clinician, particularly because it is a part of his day's work to encounter in far greater abundance the multitude of interrelationships between organic disorders or diseases and neuro-psychiatric conditions, than can possibly occur in the experience of the psychiatrist occupied mainly with the advanced stages of such conditions. With more alert appreciation of such interrelationships the physician would himself solve many of the difficulties of functional disease and organic neuroses and would be more prompt in recognizing the initial stages of the more serious psychiatric cases eventually requiring the management of a specialist.

Analyze the problems confronting you in the medical wards of a hospital or suggested by the patients presenting themselves during a single session of a busy practitioner's consulting room and you will find psychiatric factor of importance in a very large proportion of all the cases studied. The physician unmindful of these facts gropes about for evidences of organic disease in all kinds of visceral neuroses and unfortunately by reason of the accuracy of modern methods often finds enough to satisfy his mind though he has not come at all near to the real solution of his patient's difficulty. It would prolong this discussion too much to attempt even an outline of the relations to visceral neuroses of purely psychic influences left over from former life, of environmental conditions, of well founded or unfounded fears, or of the relations of disorders of the sympathetic and parasympathetic mechanisms and of pathologic endocrine glands. The subject forms a complicated and far-reaching chapter in the study of medicine and it can do no more than to mention a variety of view-points. The hope is that some day a system will be evolved which would explain everything by one or a few principles. For the moment the methods of approach are not more but perhaps rather more numerous than the old habit of relating everything to pathologic anatomy.

As the physician goes to the laboratory he will not only appreciate the varied nature of the problems but he will also appreciate the fact that the clinician will be

attracted to a closer study of the neuroses or psychoses that attend many of the definitely organic diseases with which he has daily contact. Action and reaction are here by no means always equal. A neurosis (or psychosis) secondary to an organic disease may quite overshadow the cause which gave the occasion for its occurrence. Dealt with promptly as a problem of organic disease and effectively treated, such a neurosis may readily be controlled but if allowed full development may so conceal the original cause that the physician or psychiatrist cannot well avoid a misinterpretation and misdirect much of his management. Whether seen in their earlier or their later stages such cases require a physician with a psychiatric view-point or a psychiatrist with more than ordinary clinical training.

Serious or established psychiatric problems in disease often require for their solution not only a definite point of view but more painstaking and commonly more prolonged investigation than the general clinician is disposed to give to them and also a cultivation of the technic of such investigation which he does not possess. My argument is not directed to an ignoring of the important rôle of the psychiatrist but only to emphasize the necessity of a keener appreciation of psychiatric factors on the part of the physician and a less restricted psychiatric view-point on the part of the psychiatrist.

Not to prolong my discussion too greatly let me very briefly refer by way of illustration to some of the psychiatric problems which the clinician encounters in common diseases and which he should be prepared to meet. Sometimes the cases referred to pass out of the physician's care to that of a psychiatrist, but the milder types rarely do so and are therefore possibly less familiar to psychiatrists than to internists. A much greater number of conditions might be assembled but the purpose of this discussion will be served by mentioning a few of the diseases which fall under the care of the internist and in which psychic disturbances sometimes become important features.

1 *Pneumonia* In the late stages and beginning convalescence of pneumonia, not infrequently after the temperature has become normal, more or less complete mental imbalance, disorientation, agitation, fear, rambling, etc. produce the effect of severe mental disorder that may continue for days and even stretch into durations of weeks. I have often been called upon to see patients in this condition because grave doubts have been entertained regarding the mental future of the patients. The type of such cases is more commonly of an active agitated sort than depressive and in two at least when momentarily unobserved the patient rose from his bed and leapt out of a near-by window. The mental state of the patients under discussion differs essentially from that of the pneumonia case having active delirium during the continuance of his fever and acute disease. Unlike the latter his attention may be aroused and his appreciation of his surroundings may momentarily or for brief periods be commanded but his responses are disordered and incoherent. Left to himself the patient may carry on a rambling senseless talking, sometimes interspersed with laughing or grimacing or in other cases with sudden outcries suggesting fear or pain.

The picture presented is one of acute mental disease and the question of possible encephalitis arises though there are no objective symptoms to indicate its presence

While this type of disease is usually of short duration in cases of pneumonia terminating without further pulmonary or pleural complications, it may sometimes last for weeks and in complicated migratory pneumonias and cases followed by empyema may extend to even greater duration

The prognosis when the patient recovers from the pneumonia itself has been in my experience invariably favorable

2 *Typhoid Fever* Post-typhoidal psychoses are more prone to assume a depressive type than the pneumonic and have in some instances in my experience been followed by a change of character constituting in effect a chronic psychosis of mild degree Hemiplegic and monoplegic conditions are occasionally met with during the course of typhoid and from the manner of their occurrence and clearing up as well as from the fact that vascular thrombosis is a frequent complication in this disease, it may be suspected that cerebral thrombosis may be the occasion of such occurrences as well as of typhoidal psychoses Records of such thrombosis found at autopsy have been published by Curschman, Osler, Welch and others It seems probable, however, that in transient psychoses of mild character and those appearing early in the disease (even earlier than positive diagnostic evidences of typhoid fever have come to light) less pronounced cerebral changes or purely toxic effects may be responsible for the symptoms

3 *Septic-Pyemia* Long drawn-out general infections falling under this inclusive heading are occasionally accompanied by psychic derangements that so greatly alter the usual symptomatology as to raise the question of mental derangements or focal intracranial disease Occasionally the mental symptoms occur late and outlast the evidences of active infection I recall instances in which cerebral abscess was gravely considered and operation discussed but in which the whole cerebral aspect of the infection cleared up completely without any later definite justification of even a diffuse encephalitis as the cause of the psychosis As in pneumonia and perhaps to a lesser extent in typhoid it would seem that the cerebral symptoms are toxic rather than in a gross sense organic

The cerebral manifestations of rheumatism may be cited in this same connection, are so well known that it is unnecessary to discuss them here. "Cerebral rheumatism" occurs as a part of the acute stages of severe rheumatism and is regarded as a sequel of the disease.

4 *General Debility* The occurrence of neuroses and psychoses in such conditions, though it has frequently been made the subject of medical opinion, has not as generally been recognized by physicians or neuropsychiatrists as it should be. The feeble constitution as well as the frail state of the system are what is the chief condition of women or children often who are predisposed to mental derangement and who develop in early life a less complete picture of the disease. The occurrence of the psychosis has been recorded

wholly from a neurologic or nutritional angle and the underlying factor of circulatory disease overlooked. Less often but nevertheless more than a few times have I encountered cases of rheumatic aortic regurgitation in early life, so camouflaged by neurotic manifestations that the circulatory trouble was wholly ignored.

It would be lacking in broad perspective to believe that cardiac diseases of these kinds might not operate merely as excitants of neuroses due to other causes, but there are some, and I believe not merely few, that are caused directly by the circulatory derangement.

The same types of heart disease may sometimes cause psychoses of more serious nature but my experience has been that these cases more often result from luetic aortic regurgitation and aortitis or chronic myocardial disease in later life. To what extent the luetic or arteriosclerotic changes in the cerebral vessels may contribute to the development of these cases might be worthy of consideration, but in some at least the suddenness of onset without warning suggests a circulatory explanation of cardiac origin. One or two instances may suffice.

An old servant who had had aortic regurgitation without marked symptoms and no history of decompensation suddenly while at work became violently agitated and deranged and seizing a bottle of carbolic acid drank its contents accomplishing her suicide. No previous mental disturbance and no immediate cause for her actions accounted for the happening.

An old man about 60 with luetic aortic regurgitation but no previous medical history of consequence (no great circulatory disorder and no decompensation) was sitting on a park bench with an older friend and relative whom he was visiting after a separation of years. They were reminiscing and enjoying a happy conversation when suddenly the younger man without any cause whatever rose, began to berate his old friend and became violently excited. He remained in this condition more or less and never quite fully recovered his previous entire sanity up to the time of his death a year later. This suddenness of development of the psychic disturbance, while not the rule, has at least been not infrequent in my experience, especially in the more severe forms. I shall refer to something of the same sort in connection with cerebral arteriosclerosis.

5 Cerebral Arteriosclerosis The psychology of cerebral arteriosclerosis is a chapter in medical symptomatology worthy of much more extensive exploration from the standpoint of the clinician than has ever been given to it. In 1908 I presented a brief discussion of this topic before the Association of American Physicians and though it would be easy to extend that discussion in the light of subsequent experience, it is perhaps unnecessary to attempt this here. My neurologic colleagues of that day were little inclined to lay much emphasis on the cerebral circulation as a factor in neuroses and psychoses and several of them expressed the feeling that mine was a somewhat exaggerated viewpoint. It is rather interesting to me to recall that of those who entered into the discussion the one who most fully sus-

tained my contentions was an internist of wide experience—Abraham Jacobi. I should not now recall this matter of a quarter of a century past except to emphasize that in the intervening time various sorts of cerebral conditions are more commonly recognized by neurologists as due to cerebral arteriosclerosis, and classifications of psychiatric conditions at the present time are not lacking in emphasis placed upon this etiologic factor.

Physicians who have had the continuous care of old people will find no difficulty in remembering repeated occurrences, perhaps over a period of years, of cerebral episodes in the symptomatology of such patients similar to those which I reported and which I now briefly recall. Disturbances of memory, of orientation, of character, transient aphasias, motor weaknesses, emotional instabilities, somnolence or protracted wakefulness, hallucinations and transient delusions and a great variety of additional symptoms of the same order enter into the symptom picture of sclerotic old age. More striking cases are those with convulsive attacks, complete stupor or protracted deep somnolence sometimes clearing up as quickly as they developed. Often the senile patient passes from one to another phase and clouds or clears so suddenly that one can hardly believe that any other explanation than a sudden change in cerebral circulation could account for the rapid changes. One is reminded of the swift occurrence of syncope and its prompt relief.

However much we may recognize all of these symptoms as possible results of failing or disturbed cerebral circulation, when face to face with the actual case grave suspicions of more lasting cerebral disease are certain to enter our thoughts. A few type cases may suffice to indicate the major manifestations.

An old lady under my observation almost daily from the age of 80 to the time of her death at 86 passed through periods of deep somnolence to almost complete coma lasting from one to several days and repeating themselves at intervals of some months or occasionally after shorter periods of time. There was no definite history or evidence of organic disease beyond the cerebral increase of the manifestations of advanced age. Specifically no indication of kidney disease or focal brain disease ever presented themselves. The terminal event was a protracted period of gradually deepening coma and death.

Another feature of her case was the occurrence of symptoms of marked cerebral disturbance—attacks of extreme nausea, anorexia, and regurgitation occurring regularly or periodically without cause or explanation. She was convinced that a grave organic disease of her stomach occasioned this and that she had felt this an epitaph after her death.

Autopsy revealed no organic lesion nor any significant changes in the nervous system and somewhat pronounced arteriosclerosis. No evidence of focal disease or of any sublethal character was observed.

Another case of a similar type is that of a woman over 80 years of age who had a long history of attacks of extreme somnolence and was characterized by profound

prostration, mental aberration, somnolence, stupor, and even coma without any indications of a focal brain disease. Between these attacks, which severally lasted from one or two to two or three weeks, he exhibited merely the evidences of advanced old age with feebleness as the outstanding feature but without any indications of exceptional mental senility. There were perhaps four of such attacks before the termination of his life in his ninety-fifth year.

An instance showing the rapidity of development and the equal rapidity of recovery from marked mental disorder was shown by a quite sclerotic man of 65 who, after a somewhat heavy meal, became suddenly unconscious or at least stuporous. Attempts to rouse him having failed, his physicians were summoned but were unable to discover any cause for the condition in which he was found. At the end of forty-eight hours he awoke suddenly to complete consciousness, spoke to members of his family in his room, wondering why they were surrounding him, and was thereafter as well as he had been for years before. No recurrence of this type of disturbance occurred subsequently. Nothing was discovered to connect his attack with what he had taken at his last preceding meal which was of ordinary food but perhaps a little too abundant.

6 *Gout* That preceding, during, or after severe attacks of gout mental disturbance sometimes occurs is a familiar statement in medical literature.

Two such instances may be recalled because in each of them the mental features of the case were so pronounced that they had occasioned consultation with psychiatrists who were gravely concerned regarding the mental future of the patients. In one of them it was frankly the opinion of the psychiatrist that a terminal mental state had been established.

The first of these patients was a woman of 55 who had long been suffering from chronic gout but who on this occasion was passing through a rather severe articular gouty attack involving chiefly her knees. There was high fever, extreme pain, and the other usual features. No excess of medication could be regarded as having contributed to the mental symptoms that occurred. Beginning with what appeared to be ordinary delirium not unlike that of any other fever, the patient passed into a state of mental disturbance of pronounced character persisting with unabated intensity when the temperature fell to lower levels and even disappeared. This condition lasted for several weeks before it gradually subsided and complete mental clarity was restored.

The second case was similarly a woman who had suffered with gouty arthritis of rather acute character terminating in a more subacute condition which after some weeks' duration and after the more acute symptoms had largely subsided, gave place to a mental condition that became extremely disturbing to her family. The patient was alert, wide awake, but completely disoriented and constantly talkative. After a period of ten days or two weeks, her relatives, particularly a physician belonging to her family, sought the opinion of a psychiatrist who was quite convinced that the condition was

a hopelessly established mental state. She, however, gradually became sane and remained in perfect mental health up to the time of her death except to later.

In neither of the above cases were large doses of colchicum, salicylates, opiates, or other drugs of that character given at the time of or just before the development of these mental symptoms, and it did not appear probable that drugs in any way contributed to the symptoms observed.

7 Drug Effects It is unnecessary to say much regarding the effects of the more powerful hypnotics and narcotics when freely administered but it is worthwhile to recall to the minds of internists the fact that the very moderate use of such drugs and even of far milder ones like bromides, when given continuously, at times produces alarming mental effects. No great difficulty arises in cases of patients under the regular attendance of physicians and nurses, though we are all at times slow in realizing that medication rather than other causes is responsible, but the occurrence of mental symptoms in patients who on their own responsibility have continuously taken, though not perhaps in large doses, some form of hypnotic often proves highly confusing.

It is unnecessary for me to attempt here to assemble the names of the drugs which in my own experience fall in this category, but it may very truthfully be stated that books on psychiatry could properly include a greater number of drugs among the causes of toxic psychosis than is anywhere recorded.

8 Nephritis Kidney disease is admitted among the visceral causes of neuro-psychiatric manifestations, especially when hypertension, arterial disease, cardiac disease and anemia are associated and I shall not pause to dwell on this part of the subject. There is, however, another aspect of the relation of disease of the kidneys to psychic disorders that is not so commonly recognized and may therefore merit consideration. This is the occasional development of somewhat pronounced cerebral disorders in patients suffering from slowly developed renal insufficiency with a resulting subacute or chronic anemia. Such patients at times develop a variety of mild disorders of affective type or loss of acuity, memory and other intellectual faculties that may quite over-shadow any other evidences of the underlying cause. One case of this sort in my own experience was notable because of the sudden onset of major symptom. A lawyer, known only to his family to be failing in general mental alertness, suddenly during an address to the court in support of his speech, was unable to continue and utterly lost his bearings in his surroundings. Rapidly developing evidences of kidney disease were established in a few weeks.

Psychic symptoms in prolonged secondary anemias have not been especially emphasized by investigators, and it is generally stated that may be associated with the anemia but that no psychic manifestation so definite as that described here is observed. As to cause of confusion it is not clear whether it is due to the anemia or to the state of the body in such

patients when pallor and other ordinary evidences of anemia are wanting, as they occasionally are, readily create the impression of nervous or mental disorders of other sorts

It is of course evident here as throughout the whole of this discussion that thorough-going clinical examination of all such patients and not merely a survey of their outstanding manifestations is the proper safeguard against mistaken diagnosis

Neither the clinician unfamiliar with the neurologic aspects of medical diseases nor the psychiatrist untrained in clinical medicine can properly evaluate the present state and future of such patients or arrive at a reliable opinion of the immediate prognosis. Least of all shall we obtain assistance from those who admit no backgrounds of causation for unusual types of psychic or even physical illness except subconscious states, ancient impressions, complexes and the like. With all respect for earnest workers in such fields, let us hope that they may manifest more appreciation of clinical medicine than some of them have shown, just as we hope that clinicians shall cultivate a more active interest in psychiatric points of view.

Finally let me add that internists generally should take a broader view of their responsibilities in the study and treatment of disease than has become customary in recent years. Physicians of earlier times, unsupported by specialization, often exhibited a wider point of view and it is not an unmerited criticism of modern medicine to say that in delegating to specialists the entire management of conditions in which certain localized types of symptoms have arisen, the physician not only neglects his proper duty to the patient but, as similar experiences repeat themselves, narrows his horizon of appreciation of the whole picture of disease.

THE CEREBRAL CIRCULATION*

XXV. REMARKS ON CLINICAL PHYSIOLOGY

By STANLEY COBB, M D, *Boston, Massachusetts*

IT WILL be universally agreed that blood must go to the brain if the human organism is to function mentally and physically. It is, therefore, important to know all possible facts about the cerebral circulation—in what ways it resembles circulation elsewhere in the body, and in what ways it differs. It may be stated at the beginning that all nerve cells of the central nervous system are easily injured by lack of oxygen. This sensitiveness to anemia is most marked in the most highly integrated centers, e.g. the nerve cells of the cerebral cortex. The cells of the more automatic bulbar ganglia withstand more anoxemia, the ventral horn cells of the cord even more, and the sympathetic ganglion cells are most resistant of all.² As compared to the cells of most other somatic organs, however, even these (ganglion) cells are hypersensitive to lack of oxygen.

The hydrodynamics of the cerebral circulation are unique. The brain is in a virtually closed box and is supported by a water-jacket of cerebrospinal fluid. This is not only a jacket, but fills the ventricles and perivascular spaces as water fills a sponge. The pressure of this fluid is subject to great and frequent changes. When a man lies on his side with his head at the level of his horizontal spinal canal, the fluid pressure in the whole system is normally about 150 mm of water. Immediately on sitting up, however, the pressure within the cerebral ventricles falls to *minus* 30 or 40 mm of water, while that in the lumbar sac is increased to 300 or 400 depending upon the length of the cranio-vertebral canal. Now intracranial venous pressure is always practically the same as cerebrospinal fluid pressure and rises and falls with it.^{3,4} Thus great changes in venous flow must be continually taking place within the skull, and the capillary circulation (which is the important area because it is here that the nerve cells get their oxygen) must compensate for or withstand more changes in blood flow and more sudden changes than most other organs of the body. To keep this flow adequate there must be a control of the caliber of the arterioles and an assured strong head of pressure in the arteries. To make sure of an even distribution of blood at good pressure the "Circle of Willis" (figure 1) joins the inflowing vertebral and cerebral arteries into one system, and assures blood supply even though one internal carotid artery should be occluded. Thus it is evident that the cere-

* Read at the Montreal Meeting of the American College of Physicians, February 7, 1933.

From the Neurological Unit, Boston City Hospital, Boston and the Department of Neuropathology, Harvard Medical School, Boston, Mass.

This work was aided by the Josiah Macy Jr. Foundation.

The paper is a coordination of some clinically interesting observations made in a study of the cerebral circulation during the past five years in the Department of Neuropathology at the Harvard Medical School. The titles of the original papers so far published are given at the beginning of the bibliography.

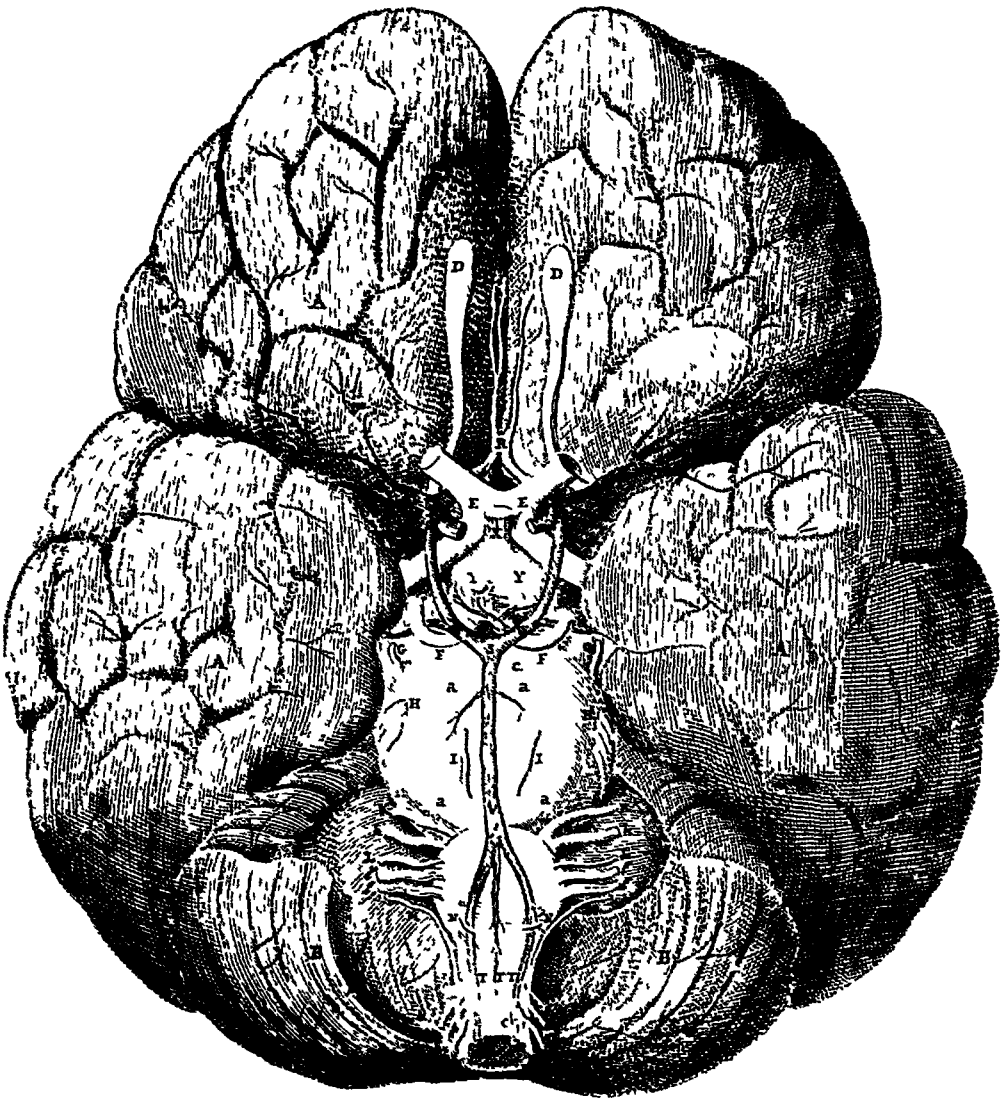
*Cerebri Inar Pag 73*Figura 1^a

FIG 1 Arteries of the base of the brain (This illustration of the "Circle of Willis" is taken from Willis' book "Opera Omnia, Amstelædani, 1682" The illustration itself was drawn by Sir Christopher Wren)

bral circulation has some especial responsibilities and some especial mechanisms with which to meet them.

Standard and conservative textbooks usually state in regard to cerebral circulation that

- (1) The arteries are "end-arteries," i.e., do not anastomose one with another, therefore, cerebral infarct is common
- (2) There is no vasomotor control, and therefore
- (3) Cerebral blood flow is regulated by the changes in general somatic blood pressure
- (4) The metabolism of the brain is low

These statements all need examination and revision

THE QUESTION OF END-ARTERIES IN THE BRAIN

The idea that all cerebral arteries are "end-arteries" arose from the fact that infarcts frequently occurred in the brain and that Cohnheim in 1872 had stated that infarcts could only occur in organs in which there was no anastomosis between arteries. Anatomical studies, however, have proved that there are many cross-connections between even the larger arteries of the brain⁵ and that the capillary bed (figure 2) of the brain is one great continuous network from occipital lobe to frontal pole.^{6,7} In spite of these vascular anastomoses, cerebral thrombosis does cause softening. The explanation is that relative anemia will cause nerve cells to degenerate, a complete anoxemia is not necessary.⁸ When an artery is occluded the blood flow is decreased in the tissue immediately supplied, the decrease in oxygen causes the capillaries to become more permeable, edema results, and the local pressure interferes with blood coming in from the nearby normal areas by way of the capillaries, for capillary pressure is low and cannot overcome even moderate obstruction. Hence the oxygen lack is increased the stasis becomes more complete, extravasation of red cells takes place, and a typical infarct is formed. It should be emphasized, however, that moderate degrees of local cerebral anemia can cause loss of function in the nerve cells affected without actual cerebral softening, the nerve cells simply change their reactions to certain stains, sections show areas of pallor (*Erbleichung*⁹), in the gross the gray matter looks slightly pale and its line of demarcation from the white matter is partially obscured. Such mild lesions are frequently all that one finds at autopsy to explain hemiplegia, aphasia, eclampsia and status epilepticus. And it should be added that few pathologists look for these mild ischemic changes. As a result many autopsies on patients suffering from these symptoms are reported as "negative." The Munich pathologists^{10,11} emphasize the importance of vascular spasm in causing such lesions, while Naffziger¹² argues that ischemia of the brain often occurs in patients with hypertension and arteriosclerosis in whom the pressure is unwisely lowered too much and too rapidly.

CIRCULATION IN ONE GYRUS

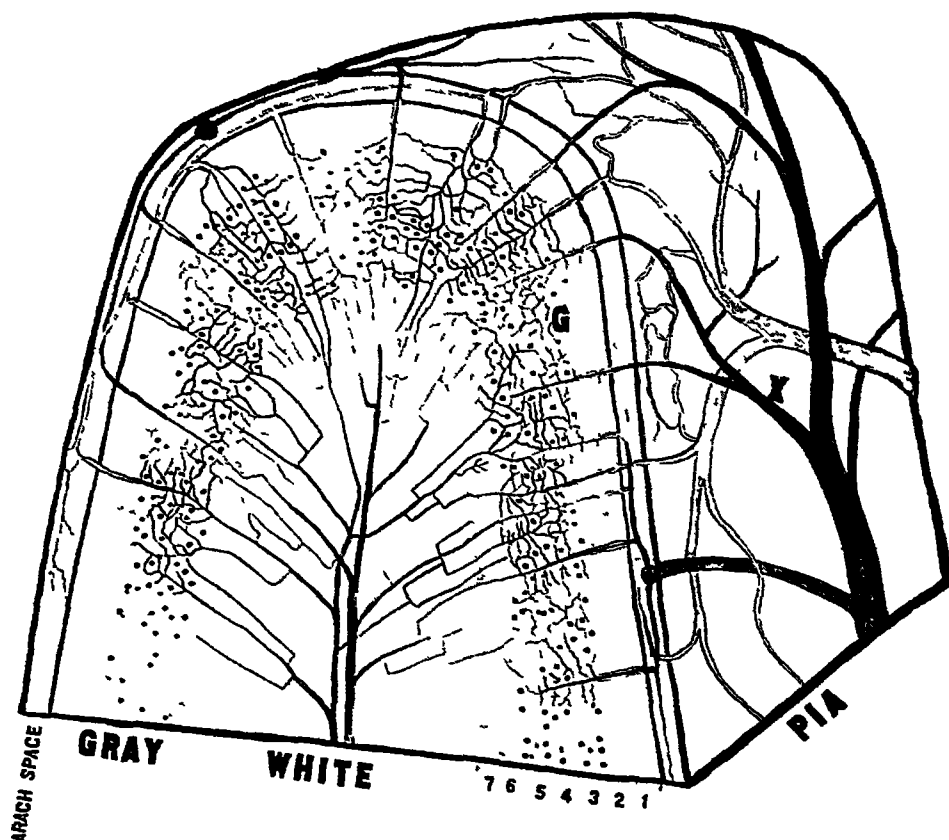


FIG 2 Diagram of the circulation in one cortical gyrus. The rich capillary bed is in the gray matter around the nerve cells, it is especially rich about the large cells in laminae 3, 4 and 5. Most of the blood supply reaches this capillary network from arterioles arising from pial arteries. Thus an occlusion at "X" would cause anemia of the gray matter at "G". The number of capillaries in the white matter is much less, and they often run parallel with nerve fibers, giving the effect of an angularly branching tree, rather than a network as in the gray matter. The venous outflow is largely outward to the pial veins (shown gray in contrast to the black arteries). A small amount of blood reaches the capillary bed by way of the deep arteries in the white matter. The cerebrospinal fluid fills the arachnoid space and enters the gray matter in sleeve-like perivascular spaces.

CEREBRAL VASOMOTOR CONTROL

It has recently been clearly demonstrated that the cerebral arteries have an autonomic nerve supply, this is true of the deep intracerebral vessels as well as of the superficial pial vessels¹³. Moreover physiological experiments have shown that there is both a vasoconstrictor and a vasodilator mechanism, stimulation of the cervical sympathetic nerve causing constriction of pial arteries, while stimulation of the vagus causes vasodilatation¹⁴. Further

study has shown that the cervical sympathetic nerve innervates only the ipsilateral cerebral hemisphere, but that the vagus has a bilateral effect.¹² Moreover, the pathway of the vagus impulses has been studied^{12, 13} and it has been demonstrated that nerve impulses may pass up either vagus nerve trunk to the medulla oblongata, leave the medulla along both facial nerves and travel as far as the geniculate ganglion and thence along autonomic nerves to the cerebral vessels. Here they cause vasodilatation. Thus, in the brain, as in other organs of the body, there is sympathetic vasoconstriction opposed to parasympathetic vasodilatation (Figure 3.) The stimulation of one vagus nerve causes a bilateral cerebral vasodilatation, whereas

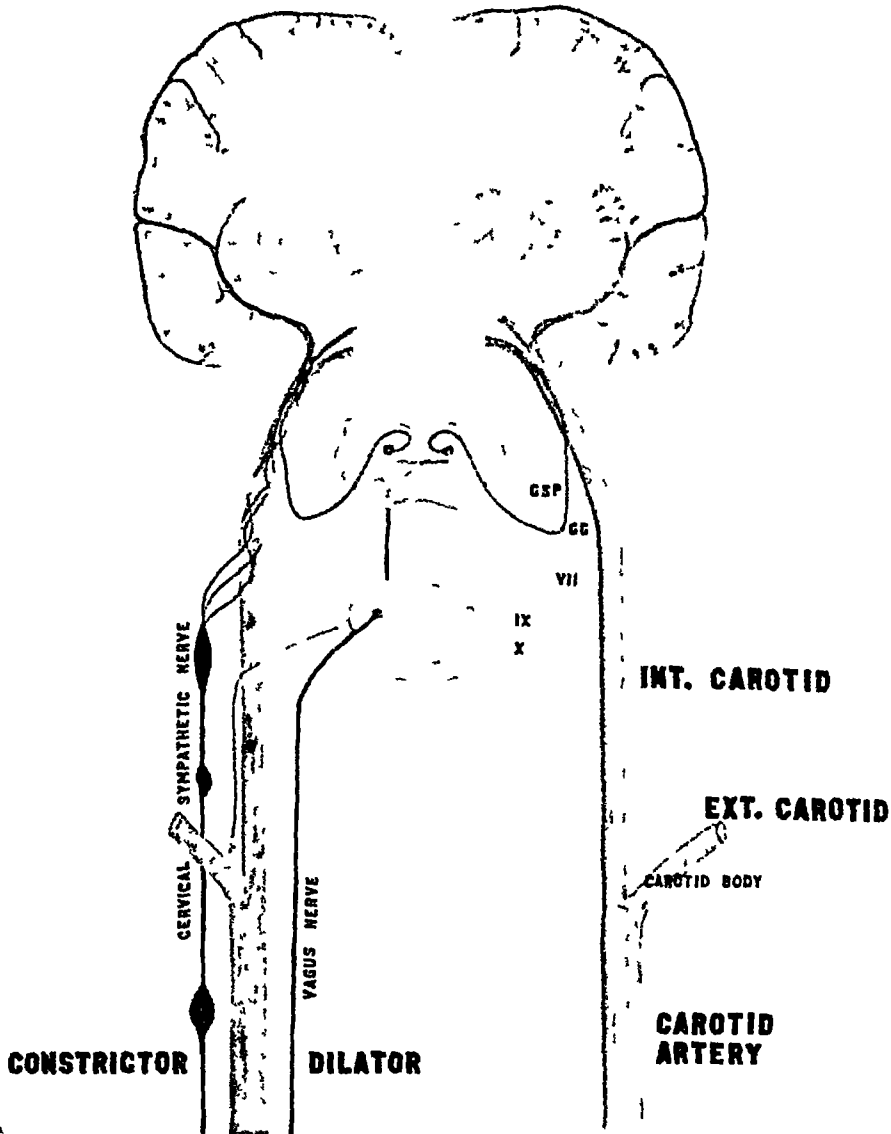


FIG 3 Diagram of the vasomotor nerve supply to the brain. The cervical sympathetic nerve sends constrictor fibers to the carotid trunk and thence along cerebral arteries, the vagus carries dilator impulses to the medulla, which pass out along the facial nerve to the internal carotid artery and its branches. Another controlling mechanism is the nerve from the carotid body which enters the medulla with the glossopharyngeal nerve.

the stimulation of a cervical sympathetic nerve causes only an ipsilateral vasoconstriction

Proving that the vasomotor system exists in the brain, as in other bodily organs, does not prove that it normally has an important function. Risei¹⁷ believes that its function is negligible. Forbes,¹⁸ who has most recently studied the question, finds that the response of the pial vessels is only about one-tenth as great as that of the vessels in the pinna of the ear to one and the same sympathetic stimulus. Putnam,¹⁹ however, by perfusion experiments shows that cervical sympathetic stimulation causes an average reduction in blood flow of approximately 15 per cent, the systemic arterial blood pressure remaining constant.

Thus there is good evidence that the cerebral vessels contract on stimulation of the cervical sympathetic nerves, that they lose tone when that nerve is cut and that they dilate when the central end of the vagus nerve is stimulated. In other words, the blood vessels of the brain react to vasomotor impulses like vessels in other organs, but less strongly. It would seem, therefore, that partial vasomotor control of cerebral vessels is now established. How important this may be for the normal function is not yet determined, and one must be guarded in drawing clinical conclusions, but the repeated demonstration of a cerebral vasomotor system certainly makes "vascular spasm" seem to be a reasonable clinical possibility under *pathological* conditions.

REGULATION OF CEREBRAL CIRCULATION BY DISTANT CHANGES IN SYSTEMIC BLOOD PRESSURE

This passive regulation of cerebral blood flow has for many years and by many authors been looked upon as the most important regulating mechanism. That such a mechanism is often effective cannot be doubted, but it should not be too greatly emphasized at the expense of other mechanisms.

Adrenalin when applied locally to the cerebral vessels of anesthetized animals usually causes a vasoconstriction¹⁴, when injected directly into the carotid artery, there may be a secondary vasoconstriction following vasodilatation, and when injected into a systemic vein there is usually cerebral vasodilatation. In other words, the local effect on the cerebral vessels is constriction, but this is overcome by the rise in hydrostatic pressure caused by the action of the adrenalin on the heart and systemic vessels. In the perfusion experiments of Putnam¹⁹ mentioned above, small doses of adrenalin apparently caused constrictions of the smaller cerebral vessels when systemic blood pressure was kept constant. Until more data are available, one must look upon the effect of adrenalin on cerebral vessels as not clearly understood, probably there is a balance between local constrictor action and general systemic pressure, the resultant being modified by the state of the organism at the time of administering adrenalin (e.g., low blood pressure, anesthesia, fear, etc.).

More continuously acting and therefore more important chemical effects are those of oxygen and carbon dioxide upon the cerebral vessels. Al-

though vasomotor influences play a part in the regulation of the cerebral blood supply, more powerful control is exercised by various chemical substances in the blood stream

Wolff and Lennox²⁵ observed pial vessels of cats under the microscope, and Lennox and Erna Gibbs²⁶ measured the oxygen content of blood taken from an artery and from the internal jugular and femoral veins of unanesthetized patients. The effect of changes in the oxygen and carbon dioxide content of arterial blood was noted in both types of experiments. It was proved that a decrease in the carbon dioxide content of the blood resulted in a moderate constriction of pial vessels in the animals, and in a decrease in the speed of cerebral blood flow in patients. An increase in carbon dioxide content was followed by a marked dilatation of vessels and an increase in blood flow. In sharp contrast an increase in the oxygen content of the arterial blood produced slight constriction and decrease in flow, while a marked degree of anoxemia showed a dilatation and increase in blood flow. Anoxemia also augmented the dilator and speeding-up effect of an increased concentration of carbon dioxide. In the human experiments it was found that changes in blood flow in the legs did not parallel changes in the brain. Oftentimes in fact, changes were in the opposite direction. The effect of carbon dioxide greatly overshadowed that of oxygen. Alterations in cerebral circulation, as measured by changes in arterio-venous differences in the oxygen content of blood, were fully as great in the brain as in the leg. The most effective measure to increase cerebral oxygen supply is the inhalation of a mixture of 90 per cent oxygen and 10 per cent carbon dioxide. The latter dilates the arteries and by inducing a condition of acidosis increases the dissociation of oxygen from hemoglobin.

Caffein (and likewise oxygen excess, alkalosis and adrenalin) is known to cause a primary cerebral vasoconstriction if given in large doses, but the reaction is modified (as with adrenalin) if the blood pressure is abnormal or if the subject of the experiment is already under the influence of other drugs.²²

Other chemical agents that will, with regularity, cause vasodilatation (in addition to carbon dioxide and acidosis mentioned above) are histamine,^{23, 27} acetyl choline, and amyl nitrite.²⁴ These agents evidently all work upon the cerebral vessels directly, for the vasodilatation usually takes place in the face of a falling systemic blood pressure.

METABOLISM OF THE BRAIN

As long ago as 1895 Leonard Hill²⁸ discussed the metabolism of the brain and stated that when compared with muscle the brain is not a seat of active combustion. Recent anatomical studies bear this out^{27, 28} for injection preparations of different organs show that cardiac muscle has approximately 11,000 mm of capillary length per cubic mm of tissue, active skeletal muscle has 6000, but at rest only 2000, the gray matter of the brain varies

from about 500 to 1000 mm of capillary length per cubic mm, while the white matter may run as low as 200

It has been shown²⁹ that the brain has a rapid blood flow in anesthetized animals, the speed being as great or greater than that of any other organ in the body (with the possible exception of the retina, which is indeed part of the brain) Calculations of the respiratory quotient of the brain have been made by Lennox³⁰ who compared the oxygen and carbon dioxide content of the blood drawn from an artery with that of blood drawn from an internal jugular vein, an arm vein and the femoral vein The average of 120 observations on the internal jugular vein gave a respiratory quotient of 0.95, while 75 observations on the femoral vein gave a respiratory quotient of 0.72 Moreover, more dextrose was found to disappear from the blood in its passage through the brain than in its passage through the extremities^{30, 31} It seems from direct experiment on brain tissue³⁷ that the brain has a rather high metabolism when compared to other organs, or to the body as a whole

CLINICAL IMPLICATIONS

Weiss³² had stated that "Today when the concept of the psychogenetic origin of psychosis dominates medicine to a large extent, recognition of the fact that somato-genetic mental symptoms, personality changes and psychoses exist, and that there is some correlation between changes in the circulatory system and the mental state, is essential to the proper emphasis of psychiatry in the larger field of medicine" I would go much farther and say that everything points to the proper oxygenation of the nerve cells as one of the most vital of human mechanisms We know little about this at present, but with new methods rapidly developing, much may be expected from the investigations of cerebral circulation That emotional stress may play an important part in the etiology of cerebral vascular symptoms is not to be doubted Syncope, migraine and convulsions all may be emotionally precipitated The exact mechanisms are as yet unknown, for observations of the cerebral vessels during life are difficult The cerebral vascular mechanism is similar to that in the skin even though quantitatively the physiological reactions differ greatly It is a reasonable speculation, therefore, that such emotional changes as are known to occur commonly in the skin may occur in a modified form in the brain Thus flushing, pallor, edema and sero-sanguinous effusions are not impossible cerebral concomitants of severe emotional stress, they all are known to occur in vascular diseases with less evanescent etiology

Clinical evidence is abundant The neurological effects of rhythmic changes in patients with Cheyne-Stokes respiration has been beautifully shown by Tournay³⁵ who found Babinski's sign present in the periods of apnea and absent when respiration was resumed Naffziger¹² has presented a strong case for the theory that lowering blood pressure in patients with hypertension and arteriosclerosis may bring on attacks of hemiplegia and aphasia More recently de Seze³⁶ emphasizes the same mechanism I have

seen several cases where such accidents have occurred after putting arteriosclerotic patients to bed and allowing a systolic pressure to fall from around 220 to about 160, reducing the blood supply to an already poorly oxygenated brain. Moreover, pressure on the carotid sinus causes a sudden fall in blood pressure in some people, and I have seen arteriosclerotic patients in whom such a fall brought on sudden syncope with convulsive movements. The psychotic episodes of cardiac patients are common experience and may be explained on a basis of cerebral hypo-oxemia.

Vascular spasm has long been a favorite clinical explanation of brief cerebral symptoms.³³ Jackson saw constriction of the retinal arteries preceding epileptic attacks, while Foerster, Penfield and others have seen actual areas of vasoconstriction in brains exposed at operation. There are also cases of Raynaud's disease with paroxysmal cerebral symptoms.³⁴ Bramwell,³⁴ Weiss³² and others have seen vasoconstriction in the retinal vessels at the onset of migraine. The list might be prolonged, but these examples suffice to emphasize to the clinician the practical importance of the experimental investigations upon cerebral circulation here summarized.

REFERENCES

I. PREVIOUS PAPERS ON THE CEREBRAL CIRCULATION

- I FORBES, H. S. Cerebral circulation, observation and measurement of pial vessels, *Arch Neurol and Psychiat*, 1928, **xix**, 751-761
- II COBB, S., and TALBOTT, J. H. Studies in cerebral circulation, quantitative study of cerebral capillaries, *Trans Assoc Am Phys*, 1927, **xlii**, 255-262
- III FORBES, H. S., and WOLFF, H. G. Cerebral circulation, vasomotor control of cerebral vessels, *Arch Neurol and Psychiat*, 1928, **xix**, 1057-1086
- IV WOLFF, H. G., and FORBES, H. S. Cerebral circulation, action of hypertonic solutions, Part I, *Arch Neurol and Psychiat*, 1928, **xix**, 73-83
- IV KUBIE, L. S., and HFTLER, D. M. Cerebral circulation, action of hypertonic solutions, Part II, *Arch Neurol and Psychiat*, 1928, **xix**, 749-755
- V WOLFF, H. G., and FORBES, H. S. Cerebral circulation, observations of the pial circulation during changes in intracranial pressure, *Arch Neurol and Psychiat*, 1928, **xx**, 1035-1047
- VI WOLFF, H. G., and BLUMGART, H. Cerebral circulation, effect of normal and of increased intracranial cerebrospinal fluid pressure on velocity of intracranial blood flow, *Arch Neurol and Psychiat*, 1929, **xxi**, 795-804
- VII TALBOTT, J. H., WOLFF, H. G., and COBB, S. Cerebral circulation, changes in cerebral capillary bed following cervical sympathectomy, *Arch Neurol and Psychiat*, 1929, **xxi**, 1102-1106
- VIII COBB, S. Cerebral circulation, quantitative study of capillaries in hippocampus, *Arch Surg*, 1929, **xviii**, 1200-1209
- IX COBB, S. Cerebral circulation, relationship of cervical sympathetic nerves to cerebral blood supply, *Am Jr Med Sci*, 1929, **clxxviii**, 528-536
- X FORBES, H. S., WOLFF, H. G., and COBB, S. Cerebral circulation, action of histamine, *Am Jr Physiol*, 1929, **lxxxix**, 266-272
- XI WOLFF, H. G. Cerebral circulation, action of acetyl choline, *Arch Neurol and Psychiat*, 1929, **xxii**, 686-690—Cerebral circulation, action of extract of posterior lobe of pituitary gland, *ibid*, 691-694—Cerebral circulation, action of amyl nitrite, *ibid*, 695-699

- 1 RISER, M. P., MERIEL, P., and PLANCHES. Les spasmes vasculaires en neurologie. Etude clinique et expérimentale, *Encephale*, 1931, xxvi, 501-528
- 2 FORMES, H. S. Personal communication
- 3 PUTNAM, T. J. Personal communication
- 4 WEISS, S., ELLIS, L. B., and ROHM, G. P. Body responses in man during the continuous intravenous administration of histamine, *Am. Jr. Physiol.*, 1929, xc, 551-552
- 5 LOMAX, J., and MYERSON, A. Action of certain drugs on cerebrospinal fluid and on internal jugular venous and systemic arterial pressures of man. *Arch. Neurol. and Psychiat.*, 1932, xxvii, 1226-1244.
- 6 See cerebral circulation XVIII
- 7 See cerebral circulation X
- 8 See cerebral circulation XI
- 9 See cerebral circulation XII, XVI and XX
- 10 HILL, L., and NABARRO, D. N. On the exchange of blood gases in brain and muscle during states of rest and activity, *Jr. Physiol.*, 1895, xvi, 218-229
- 11 KROGH, A. Anatomy and physiology of capillaries, 1924, Yale University Press, New Haven, Conn.
- 12 See cerebral circulation II
- 13 See cerebral circulation VI
- 14 See cerebral circulation XIV
- 15 MYERSON, A., and HALLORAN, R. D. Studies of biochemistry of brain blood by internal jugular puncture, *Am. Jr. Psych.*, 1930, x, 389-406
- 16 WEISS, S. The interaction between emotional states and the cardiovascular system in health and disease, *E. Libman Anniversary*, 1932, iii, 1181-1198
- 17 COBB, S. Causes of epilepsy, *Arch. Neurol. and Psychiat.*, 1932, xxvii, 1245-1263
- 18 BRAMWELL, E., and McMULLIN, W. H. Discussion on migraine, *Brit. Med. Jr.*, 1926, ii, 765-775
- 19 TOURNAY, M. A. Respiration de Cheyne-Stokes et signe de Babinski périodique, *Rev. Neurol.*, 1927, i, 356-358
- 20 OSLER, W. The cerebral complications of Raynaud's disease, *Am. Jr. Med. Sci.*, 1896, cxii, 522-529
- 21 HOLMES, E. G., and SHERIF, M. A. F. Relationship between sugar in blood and lactic acid in brain, *Biochem. Jr.*, 1932, xxvi, 381-387

THE EVIDENCE FOR A CEREBRAL VASCULAR MECHANISM IN EPILEPSY*

By WILDER PENFIELD, M D , F R C S C , *Montreal, Canada*

THE MECHANISM of so prevalent a cause as epilepsy must necessarily interest every physician. The suggestion that vasoconstriction plays a rôle in the spread of an epileptic discharge is to be found in the prescient writings of Hughlings Jackson¹ and he himself reported vasoconstriction in retinal arteries during an epileptic seizure. Spielmeyer² has found histological evidence of recurring vasospasm in the brains of epileptic patients. Foster Kennedy³ reported visible shrinking of the brain in an epileptic attack seen at the operating table and Foerster,⁴ who has observed many fits during intracranial operations, reports that the brain shrinks, then expands enormously with cyanosis of the pia. He also mentions an anemia which may spread outward from the focus.

The blood vessels of the pia mater, like vessels elsewhere, are under the control of the sympathetic nervous system as finally demonstrated by Forbes and Cobb. These vessels, moreover, have a further control, parasympathetic in type, as demonstrated by Cobb and Finesinger⁴ and by Chorobski and Penfield⁵. Furthermore the blood vessels within the brain bear perivascular nerves which suggest that they too are capable of constriction and dilatation (Penfield⁶). The physiological observations which indicate nervous control of cerebral blood vessels have all been made upon experimental animals.

This is to be a report of 30 examples of epileptic seizures in conscious human patients who lay with one cerebral hemisphere exposed to view on the operating table. The immediate reaction of a practical physician to this statement may be to inquire, "Why did you operate upon these patients and what were the results?" The results so far have justified the procedure but they will not be analyzed in print until sufficient time has elapsed for reasoned judgment. There have been, so far, apparent complete cures and apparent complete failures. I shall report here only certain observations made in the course of operations, for after the opening, we usually devote an hour or two to study and observation of the brain before proceeding with any operative manoeuvre.

On first seeing an epileptic patient we study him to discover whether or not his attacks have a focal pattern. If so we usually carry out encephalography. If this indicates a focal lesion and if the location of that lesion is such as to produce a seizure of the particular pattern which the patient presents we are apt to raise a large osteoplastic bone flap to inspect the brain. This done, a convulsion is usually induced by stimulation. Watching the brain during the epileptic seizures sometimes guides one to intelligent therapy, whether it be excision of a local focus, ligation of an artery or some-

* Read before the American College of Physicians, Montreal, February 9, 1933

thing else. It has at the same time demonstrated to us phenomena associated with epilepsy which before were no more than dark conjecture.

CASE I

A boy of thirteen years complained of local or Jacksonian epilepsy which affected the right hand and was often confined to that member. Osteoplastic craniotomy showed, to our disappointment, no gross lesion. I will quote from my note written immediately after operation: "Galvanic stimulation of the post-central gyrus (at 3, figure 1) near the fissure of Sylvius, produced invariably numbness of the mouth,

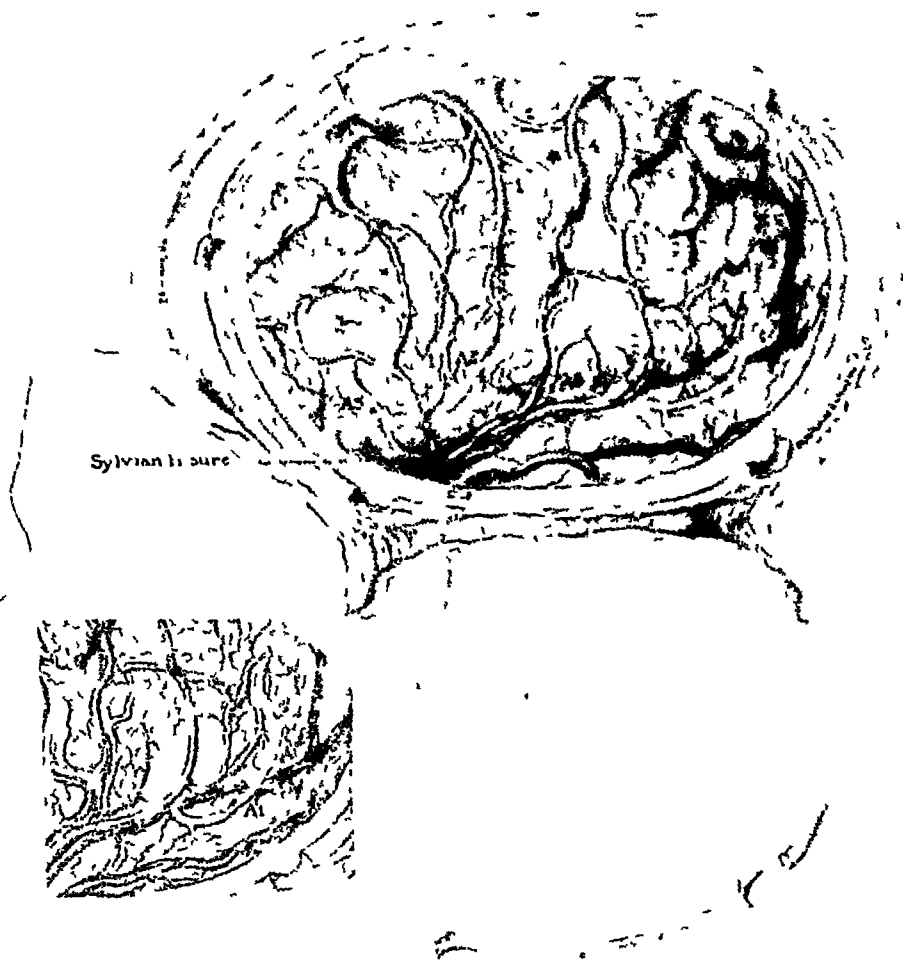


FIG 1 Case 1 Left osteoplastic craniotomy. For reference to numbers see text. The pallor appeared during a seizure produced by stimulation at 1. The inset shows the arterial constriction which appeared spontaneously after the seizure.

both sides. Stimulation of the post-central gyrus at 4 produced a clonic movement of the whole right arm accompanied by a sensation in his arm, a fact which was verified by repeating the stimulus a number of times. Movement of hand and arm were produced by stimulation of the pre-central gyrus at 1 and 2. Stimulation of the other parts of the cortex with equal intensity gave no result.

"During this exploration there were no particular changes in the appearance of the cortex. A faradic stimulus was then used just sufficient to give a twitch in the exposed temporal muscle. Various areas about the cortex were stimulated without

result and some of the large arteries were also stimulated, without result. When the post-central gyrus was stimulated faradically at point 4 clonic movements of short duration were produced as previously, but the movements went a little further, becoming somewhat convulsive in character. It was likewise noted following this that the area about the stimulation became pale. After this effect had worn off the motor gyrus was stimulated in front of this point at 1. This resulted in a convulsion of considerable duration. During this time a zone which included most of the motor gyrus and some of the post-central gradually became quite pale, while the brain surface posteriorly and anteriorly and all the way forward to the frontal pole became red and suffused (figure 1).

"During the attack the brain was watched closely. No pulsation whatsoever could be seen in the arteries. The veins gradually became bluer and some of them almost black. The contrast between the motor area and the suffused area was striking. As the attack subsided pulsation could be seen again in the arteries, at first slightly and then with the cessation of all convulsive movements all the arteries were seen to pulsate violently.

'At this time a strange phenomenon was noted. The artery marked A1 showed a definite constriction. This was so sharp that it could not be doubted. The lumen was practically closed at this point (figure 1, inset). Proximal to this constriction the artery was pulsating. Distal to it no pulsation could be seen with the naked eye. There was no particular change in the color of the artery. Over a period of about ten minutes this constriction gradually passed off. At one time there persisted at the site of the previous constriction a little pallor but this eventually disappeared also.

"The initial convulsion was followed by several other wandering convulsions of different pattern. In the second such seizure, which was observed by Dr. Cone, the eyes turned, he said, in a strong, steady gaze across to the right. At the moment that this was reported we noted on the surface of the brain that a white zone had appeared in the vicinity of the artery A1 (see inset). The rest of the brain, even including the motor area, was now more or less suffused. This attack which was characterized as mentioned above by turning of the eyes slowly to the right, was also associated with clonic twitching of the eyelids. (The anemic zone was not far from the occipital field for eye turning.) During the next ten minutes varying areas of the brain were seen to become blanched and other areas suffused. The changes from a good color to blanching occurred in the almost imperceptible way that a cloud shadow may be seen to cross the landscape on a sunny day. Sometimes the appearance of anemia or blanching was associated with a renewed convulsion, sometimes not.

"The patient continued to have convulsions of varying types until it was deemed best to terminate them. He was then given ether. Shortly following the administration of ether the whole cortex became somewhat suffused and the motor area less pale. This made the brain become practically the same color throughout."

It is seen therefore that the above arterial constriction appeared after an epileptic seizure which involved a large part of the hemisphere. It was as this constriction was disappearing that the neighboring cortex became rather suddenly blanched. In this case blanching of cortex seems to have been associated directly with the local seizure. In other cases such blanching has appeared as a sequel to the attack.

CASE II

A second case may be mentioned quite briefly. A young girl aged 18 was referred to me by Dr. Rawle Geyelin of New York. She was suffering from epileptic seizures which apparently arose first in the left hemisphere. Operation was decided upon for reasons which will not be discussed at present. An attack which was typical for her was induced by faradic stimulation of the frontal cortex, well anterior to the motor gyrus and close to the midline. Coincident with the attack the brain became

blue, the arteries stopped visible pulsation and likewise became darker. There appeared two small patches of comparative anemia just above the fissure of Sylvius. When these were noted the convulsive movements had disappeared everywhere except in the right side of the face. This continued a little longer. It was then seen that one of the two arteries which passed over these anemic areas showed a point of constriction. The convulsive movements ceased and did not return, the anemia faded

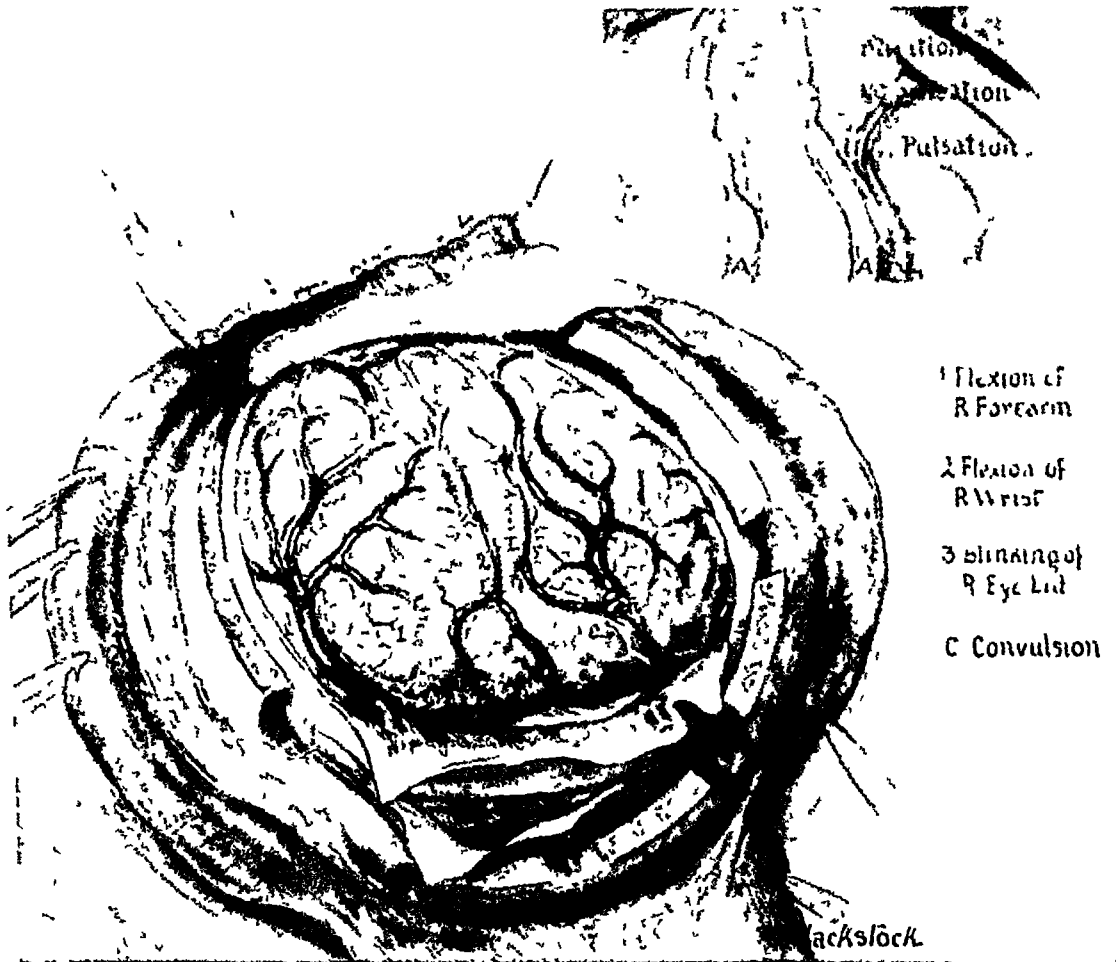


FIG 2 Case 2 Left osteoplastic craniotomy. An attack was produced by faradic stimulation at point C. Following this the arterial constrictions indicated in the inset appeared in two arteries which originated in the fissure of Sylvius and passed upward over the cortex.

However, from then on for the next half hour these two arteries continued to show varying patterns of constriction. At one time there was a definite bologna sausage appearance in both. As indicated in figure 2 there was visible pulsation on either side of the double constriction, but not between the two constrictions.

CASE III

A young girl complaining only of recurring Jacksonian epileptic seizures on the left side of the body was referred to me by Dr W F Hamilton. She was found to have an infiltrating glioma of the right frontal lobe as indicated in figure 3. After inducing a seizure by stimulation at *r* a constriction, as shown in the inset of figure 3, developed and persisted some time.

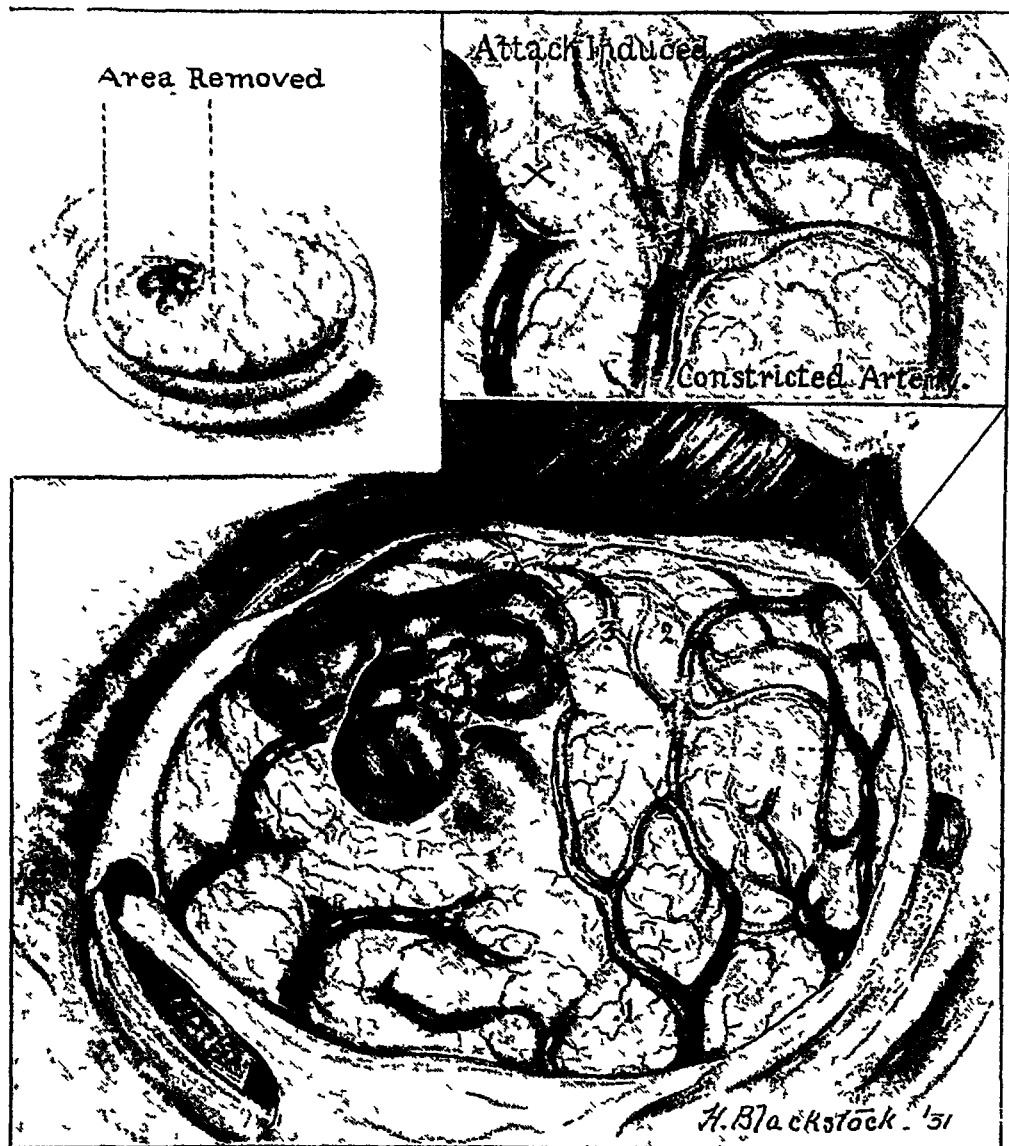


FIG 3 Case 3 Right osteoplastic craniotomy Galvanic stimulation at 1 (5 milliamperes) produced flexion of left hand, at 2 a sensation of taste (5 ma), at 3 twitching of the mouth Stimulation at 4 (9 ma) produced an epileptic seizure Constriction of artery indicated in inset appeared after attack

DISCUSSION

In preparing this study I have reviewed 43 operations in which electrical stimulation of the brain was carried out Of these cases seizures were produced in all but 13 cases* In none of these 13 cases of stimulation without attacks did there appear arterial constrictions, areas of anemia, flushing or other vasomotor manifestations This may serve to some extent as a control

* Four of the failures may be explained by the fact that the site of stimulation was far frontal or occipital, sites from which we have never yet succeeded in producing a convulsion In four cases stimulation was used only for localizing purposes

In 30 cases stimulation was followed by an aura, a local attack or a generalized attack. In only four of these no vascular change was recorded, three being auras only and of the other the record was incomplete. The remaining 26 cases all presented striking vascular changes and all but six showed some alteration in cerebral blood vessels or in vascularization as sequel to the attacks.

During the seizure the almost invariably associated phenomenon is the arrest of visible pulsation in the arteries of the brain, and we employ magnifying lenses to observe these vessels. This cessation of pulsation is usually wide-spread and in such cases it has been observed on several occasions that the radial pulse also disappeared completely for a corresponding period. Such a phenomenon indicates that discharge from the cerebral autonomic centers has affected the vasomotor organization of the whole body. But I do not think there is always such a generalized vascular response. In four cases the arterial pulsation was definitely reported as stopping only in a local area near the stimulation and here the seizure was, of course, a local one.

It should be further noted that stimulation caused a gyrus to blush immediately on three occasions, twice it was the post-central and once the pre-central gyrus. The response on the part of the patient was slight in these cases and probably not to be considered convulsive.

In general, the arteries may become blue like the veins during an attack. If there is respiratory difficulty the veins are apt to be very full and venous pressure high, so that there occurs troublesome bleeding from various veins from which hemorrhage had been previously arrested. When bulging of the brain occurs it is doubtless due to this respiratory embarrassment. In the absence of such embarrassment I have seen the veins collapse during a seizure while the arteries became gradually blue.

Most of the findings therefore suggest that very little blood is passing through the capillary bed of the brain during the actual seizure.

VASCULAR SEQUELAE

A Dilatation of Capillary Bed. After the attack the cerebral arteries pulsate violently and I believe more rapidly than before operation. Their color becomes a bright red and arteries which were not seen to pulsate before the seizure may now begin to do so visibly. In fact this recovery may go so far that the veins themselves take on an arterial hue. In four cases the reddening of the veins after the seizure was so marked that they approached in color the bright red of the arteries.

One extreme example of this may be cited. It was a case of focal epilepsy where we found no gross focal lesion. After extended galvanic exploration a faradic stimulus in the motor area produced a unilateral seizure. One minute later my assistant, Dr. Thomas Hoen, called my attention to a curious stripe in some of the larger veins. An amazing change had taken place. The central portion of the parietal lobe was redder than the rest of the brain. This zone was bounded by large veins.

Into the tributaries of these large veins was flowing arterial blood from this reddened zone, while into the tributaries from the outlying brain was flowing dark venous blood. The result was that the outer half of each vein was dark blue and the inner half bright red, the two streams maintaining their separation as when a muddy tributary joins a clear river and fails to mix for a long distance. When the patient was asked to cough it was noted at the Y-shaped junction of a red and blue vein that red blood was forced down a little way into a blue tributary as though the pressure resistance in the red branches was greater than that in the blue*. In such cases it must be concluded that the blood is passing rapidly through a widely opened capillary bed or that the tissues for the time being are incapable of taking up oxygen.

B Cortical Anemia The most frequent sequel to convulsion is not vascular dilatation but the appearance of focal areas of cortical anemia (nine cases). These may appear during the seizure but usually develop imperceptibly afterwards, indicating areas which have been the site of epileptic discharge. In one case operated upon three years ago multiple anemic spots up to 7 mm in diameter developed upon the cortex within the general distribution of a large artery. Ligature of this artery resulted in immediate paralysis of those functions disturbed first in the inauguration and spread of his fits. The paralysis was temporary and has been followed by complete cessation of his attacks up to the present.

You are all familiar with the post-epileptic paralysis which sometimes follows a seizure and which is usually located in the involved part. This paralysis is doubtless to be explained by these associated vasomotor changes and certainly not on the basis of simple fatigue. The paralysis develops at times without a preceding convulsion. In such cases it is evidently due to spontaneous vasoconstriction. In two epileptics I have seen cortical anemia appear spontaneously.

C Spasmodic Closure of Large Arteries Six cases showed constriction of one or more pial arteries, a constriction which shut off the vessel completely. It may be at one point or it may extend a long distance, or there may be multiple constrictions. These constrictions remain from 15 to 30 minutes as a rule, fading out gradually.

In one case arterial constriction appeared *before* a frank convulsion but after stimulation, and in one case it seemed to appear spontaneously and without being associated with convulsion.

In conclusion, the one constant, visible phenomenon in the brain during an epileptic seizure is cessation of arterial pulsation. Pallor may be present during a seizure but more often follows it. The epileptic brain is subject to local vasomotor reflexes such as have never been described in the normal

* A word of warning may be added here. On the day following operation this patient developed aphasia and some weakness of the right side although her speech was normal all through the operation. The aphasia cleared only after two or three weeks.

Galvanic stimuli should never exceed 12 ma and faradic stimuli should be no greater than the weakest current capable of causing contraction in the exposed temporal muscle.

brain These changes further cannot be reproduced in animals according to as yet unpublished work carried out by Lyle Gage in our laboratories Physiological instability of the blood vessels seems to be the abnormal state common to epileptics of all varieties

From the point of view of therapy the easy surgical conclusion that cervical and dorsal sympathectomy should therefore make epilepsy impossible, unfortunately does not hold In four carefully controlled cases I carried out complete sympathectomy without abolishing epileptic seizures, although it seems to have helped one patient greatly Gage has found the same to be true of experimental epilepsy in animals Attacks can be induced in them even after complete sympathectomy

The vasomotor spasms and changes seen so characteristically in the cerebral cortex of epileptics are due to vasomotor reflexes but reflexes which are probably *not* subserved by autonomic neurones placed outside of the cranial cavity They seem to be subserved by such nerve cells upon the blood vessels of the brain and by a local vascular nerve plexus which I believe, from histological studies, to be significantly increased in some cases at least Where such a lesion exists, excision of a focal scar with its vascular plexus is at present the most effective way of abolishing these malignant local reflexes

BIBLIOGRAPHY

- 1 The selected writings of John Hughlings Jackson, 1931, Ed Taylor, London
- 2 SPIELMEYER, W The anatomic substratum of the convulsive state, Arch Neurol. and Psychiat, 1930, xxiii, 869
- 3 FOERSTER, O, and SPIELMEYER, W Die Pathogenese des epileptischen Krampfanfalles, Deutsch Ztschr f Nervenhe, 1926, xciv, 15
- 4 COBB, S, and FINESINGER, J Cerebral circulation XIX The vagal pathway of the vasodilator impulses, Arch Neurol and Psychiat, 1932, xxviii, 1243
- 5 CHOROBSKI, J, and PENFIELD, W Cerebral vasodilator nerves and their pathway from the medulla oblongata with observations on the pial and intracerebral vascular plexus, Arch Neurol and Psychiat, 1932, xxviii, 1257
- 6 PENFIELD, W Intracerebral vascular nerves, Arch Neurol and Psychiat, 1932, xxvii, 30

THE VALUE OF ALIMENTARY GALACTOSURIA IN THE DIAGNOSIS OF JAUNDICE*

By HENRY J TUMEN, A B , M D , and GEORGE MORRIS PIERSOL, B S ,
M D , F A C P , *Philadelphia, Pennsylvania*

THE INCREASE in our knowledge of hepatic physiology has led to a multiplicity of tests of liver function. It is now possible to find reports of the most diversified methods for evaluating the condition of this organ. The activities of the liver in the metabolism of fats, carbohydrates and proteins, its power to excrete bilirubin and various dyes and its ability to store water have all been utilized for this purpose. Although it is realized that the various functions of the liver may be unequally disturbed by disease and that a single functional test may therefore occasionally fail, the necessity for the multiplicity of tests proposed has been questioned¹. It is felt by some that we already have sufficient means to show in a general way whether or not the liver function is disturbed and that the present need is for a method of examination which will aid in the differential diagnosis of the type of disturbance which exists. Of the tests now available, one, the production of alimentary galactosuria, seems to offer definite assistance in differentiating the types of jaundice and it is with a discussion of the value of this test that this paper is concerned.

The carbohydrate metabolic activity of the liver has been studied in many ways. The production of alimentary glycosuria, the glycemic response to adrenalin, the metabolism of lactic acid, studies of the blood and urine sugar after the ingestion of levulose and galactose and, recently, the response to the combined administration of insulin, glucose and water² have all been utilized in a study of this aspect of liver function. It is unnecessary to consider the theoretical and clinical features of all of these tests. However, in order to evaluate the results of our studies, we will briefly review the present knowledge of galactose metabolism.

In 1899 Sachs³ demonstrated that to remove the liver from frogs markedly lowered their tolerance for levulose although they still were able to handle glucose and galactose satisfactorily. Strauss,⁴ in 1901, first used levulose to study liver function in human beings and demonstrated a decrease in levulose tolerance in the majority of patients with liver disease. This finding was rapidly substantiated by many workers and within a relatively short time the levulose test of liver function was being widely used. Within recent years, however, this test has lost some of its popularity and has now, except in England,⁵ been largely superseded by the use of galactose. The use of this sugar in the study of hepatic function was first suggested by Bauer,⁶ in 1906.

* Read at the Montreal Meeting of the American College of Physicians, February 8, 1933. From the Medical Wards and the Gastro-enterological Clinic of the Hospital of the Graduate School of Medicine of the University of Pennsylvania.

There is ample theoretical background for this use of galactose. Its utilization principally by the liver was demonstrated by both Draudt⁷ and Fischler,⁸ who showed that when the sugar is fed to dogs with an Eck fistula from 80 to 85 per cent of the galactose is excreted in the urine. Bollman, Power and Mann⁹ state that the same amount is excreted by dogs whose livers have been removed. Mann and Magath¹⁰ studied the relative value of various sugars in relieving the hypoglycemic shock caused by hepatectomy and found that the liverless animal could not use galactose. That the intestines are not necessary to the utilization of galactose was shown by Worner,¹¹ who states that the tolerance toward this sugar is the same whether it be given by mouth or injected into a branch of the portal vein. Foster¹² showed that a very small difference exists between the arterial and venous blood sugars after galactose feeding, and felt that this indicated that the sugar is not used in the muscles.

The relative ease with which galactose forms glycogen in the liver has been subject to some question. Brocard,¹³ for instance, felt that galactose and levulose were utilized with equal ease by the liver. Most workers, however, state that galactose forms glycogen poorly. Foster,¹² believed that the marked hyperglycemia which occurred after this sugar was given indicated that the liver had difficulty in absorbing it. Isaac and Adler¹⁴ demonstrated by perfusion experiments that the liver does not easily form glycogen from galactose. This opinion was also expressed by Abderhalden,¹⁵ Hofmeister¹⁶ and, more recently, by Cori.¹⁷

At the present time it is generally felt that there is no kidney threshold for galactose. Folin and Berglund¹⁸ were able to find the sugar in the urine after giving quite small doses. Harding and Van Nostrand¹⁹ after careful blood studies, concluded that no threshold exists for this sugar, this is also the view of Bloch and Weisz.²⁰ This point is important because if a threshold is present, its variation would affect the amount of galactose passed by different individuals. Because galactose is very rapidly absorbed it is difficult to correlate the sugar findings in blood and urine specimens, and although it is probable that no threshold exists for galactose, this point is not completely settled. Halberkann and Kahler²¹ have shown that galactose is excreted unchanged in the urine.

In discussing the value of galactose in testing liver function it is important to consider the influence of insulin on the assimilation of the sugar. Wierzuchowski²² reported that insulin reduced the amount of galactose passed in the urine. Corley,²³ however, stated that although insulin caused galactose to disappear rapidly from the blood the degree of galactosuria was unaffected. Basch and Pollak,²⁴ Weltmann,²⁵ and Bloch and Weisz²⁶ also felt that insulin had little or no effect on the utilization or excretion of the sugar. The earlier work on this point is subject to some question since differentiation of the blood sugar into glucose and galactose was not done. This criticism, however, does not apply to the recent work of Roe and Schwartzman,²⁷ who made separate determinations of these two sugars.

They showed that even toxic doses of insulin do not change the rate of removal of galactose from the blood of rabbits and that galactose is not a direct physiological antagonist to insulin

Theoretically, therefore, galactose, which is utilized exclusively, though with difficulty, by the liver, which is probably without a kidney threshold and the metabolism of which is uninfluenced by insulin is a suitable substance with which to test the function of the liver

Bauer's original papers stressed the occurrence of excessive alimentary galactosuria in cirrhosis⁶ and in catarrhal jaundice²⁸. This was not found in cases of jaundice due to obstruction. That it is parenchymal liver damage which lowers the tolerance to this sugar was shown by Roubitschek,²⁹ who induced phosphorus poisoning in animals and found an increase in galactose excretion. The test was soon applied clinically and Bondi and König,³⁰ Reiss and Jehn,³¹ Worner and Reiss,³² Hatiegan,³³ and others^{34, 35, 36, 37} reported a definite degree of success in diagnosing hepato-cellular jaundice by means of alimentary galactosuria. These authors agreed that the test was usually positive in jaundice due to parenchymal liver damage and usually negative in jaundice due to obstruction. Many of them state that the use of galactose gave more accurate results than the use of levulose. In 1919 Worner³⁸ summarized many of the previously reported cases in the statement that excessive alimentary galactosuria was present in 80.5 per cent of catarrhal jaundice and in 68 per cent of obstructive jaundice. He and others concluded that a positive response to the test indicated the existence of diffuse parenchymal damage to the liver. The diagnostic value of the test, however, has not been unquestioned. Rouillard³⁹ stated that tolerance for both levulose and galactose is influenced by extrahepatic factors, and that tests based on the use of these sugars are unreliable. Frey⁴⁰ looked upon the galactose test as unsatisfactory, but used too small a dose of the sugar for accurate conclusions. Jacoby,⁴¹ Faltitschek and Krasso,⁴² Beckmann⁴³ and others reported cases of liver disease with normal galactose tolerance. However, a review of these reports indicates that even though alimentary galactosuria may be absent in many undoubted cases of hepatic damage, such as cirrhosis, severe congestion, and malignancy, these are usually cases of chronic or circumscribed liver disease and that the test is frequently positive in patients with catarrhal jaundice or toxic hepatitis. On the other hand, Althausen and Mancke² reported 10 cases of catarrhal jaundice only two of which were positive to the galactose test.

Some of the lack of agreement in previously published reports is undoubtedly the result of an absence of uniformity in technical procedures, such as the dose of sugar used and the length of time over which urine is collected. There has also been no universally recognized criterion for a positive result. Bauer recommended the administration of 40 grams of galactose since he found that the normal tolerance was between 20 and 40 grams and that with doses of less than 40 grams most normal individuals and many of those with liver disease would assimilate the entire dose of the

sugar. Strauss¹¹ found sugar in the urine only twice after 37 normal individuals had been given 30 grams of galactose. The use of a dose of 40 grams of the sugar was advised by Worner and Reiss,¹² Bloch¹³ and also by Schellong¹⁴ who was able to demonstrate an absence of galactosuria in a case of arsenical jaundice if smaller doses were used. Reiss and Jehn¹⁵ noted no relationship between weight and liver function and Meyer and Stern¹⁷ found that the galactose metabolism of children is similar to that of adults. Rowe¹⁸ has studied galactose tolerance in a large series of patients, mostly without liver disease, and feels that the tolerance to this sugar is not related to age, weight or body surface. He does feel, however, that there is a definite difference between the sexes in the ability to utilize galactose and that women have a somewhat greater tolerance than men. Rowe states that the assimilation limit for normal men is 30 grams but for women prior to the menopause it is 40 grams. This difference is ascribed to the activity of the mammary gland. A review of the cases reported does not bear out this contention of Rowe, for the amount excreted after a 40 gram dose of galactose seems entirely independent of the sex of the patient. It must be recalled, however, that Rowe's method of examination is purely qualitative and that he regards as positive the presence of sufficient sugar in the urine to cause a positive Benedict's reaction. It is not entirely accurate, therefore, to compare his results with those obtained from quantitative sugar determinations. A possible explanation for the discrepancy which exists between the opinions of Rowe and others may be found in the work of Harding and Moberley⁴⁹. They state that women seem to have a greater diuretic response to water than do men. For that reason the urine passed by women after the ingestion of sugar solutions is more dilute and more sugar must be taken by women to give a positive Benedict's test. If, therefore, the result of the qualitative Benedict's test is used as a criterion for sugar tolerance one might be led to the conclusion that women have a greater tolerance for galactose than do men.

At the present time 40 grams is the accepted dose of galactose for the testing of liver function. As has been mentioned, Frey⁴⁰ used only 20 grams, while Hirose⁵⁰ administered 25 grams. It is obvious that results from their series cannot be compared with those obtained when the larger dose is used.

There is also some disagreement as to the period over which urine should be collected after the ingestion of the sugar. In most instances, urine contains galactose for no longer than four or five hours so that we have terminated our studies after five hours. This follows Bauer's original recommendation. Many collect the urine for two six-hour periods³¹. Fiesinger and Thiebault⁵¹ advise examining the urine for 24 hours after the galactose is taken. Wagner³⁷ examined hourly specimens until two which were sugar-free were obtained. Bauer⁵² has more recently adopted this method since he feels that the oliguria occasionally seen in cirrhosis may cause delay in the excretion of the sugar.

There are great differences in the degree of galactosuria which the various authors consider as a positive indication of liver disease. Schellong⁴⁶ and Wagner³⁷ feel that excretion of more than one gram after taking 40 grams of galactose should be regarded as indicating disturbance of hepatic function. Brugsch⁵³ looks upon 1.5 grams as the most a normal individual will excrete. Bondi and König,³⁰ Worner and Reiss,³² Neugebauer,³⁴ Davies,⁵⁴ Kahler and Machold,⁵⁵ and Sisson³⁵ diagnose liver dysfunction if two grams are excreted. Bode⁵⁶ and Elek and Oppenheimer⁵⁷ are more conservative and feel that patients with normal livers may excrete up to three grams. Jacoby,⁴¹ on the other hand, did not use a quantitative test but based his conclusions on the duration of the galactosuria. Fiessinger and Thiebault⁵¹ feel that the concentration of the excreted sugar and not the amount is important. They state that a normal individual who takes 40 grams of galactose and then not more than 1500 c.c. of fluids within the next 24 hours should pass the sugar in a concentration of 0.1 per cent or less. If hepatic disease is present the concentration may reach 1 per cent.

Such diversified standards can lead only to confusion. We feel that the most accurate and conservative diagnostic evaluation is that of Bauer who emphasizes the amount of sugar passed. He feels that the excretion of two grams or less of a 40 gram dose of galactose is normal, and such a result is considered negative. An excretion of between two and three grams is weakly positive and is suggestive of the presence of liver disease, while the passage of more than three grams is strongly positive and indicates that liver disease is definitely present. We have used this evaluation in reviewing our own cases.

In 1922 Kahler and Machold⁵⁵ recommended that a study of blood sugar response be substituted for urinary excretion in determining the galactose tolerance. They were led to do so by their failure to obtain a pathological degree of galactosuria in cases of cirrhosis. They also felt that examination of the blood sugar eliminated the renal factor which entered into the older method, since they believed that kidney disease could interfere with excretion of the sugar and cause false negative results. This last point is still unsettled. Corley²³ was unable to show any decrease in galactose excretion after producing experimental nephritis and he could not increase the excretion by causing phloridzin diabetes.

Folin and Berglund¹⁸ have reported that hyperglycemia does not occur after galactose ingestion but this has not been confirmed. Foster¹² and Bodansky⁵⁸ showed a marked rise in blood sugar after feeding galactose to animals, the latter demonstrating that this sugar caused more glycemic response than either levulose or glucose. Kahler and Machold,⁵⁵ using the degree of hyperglycemia after galactose feeding as the criterion, reported a higher incidence of positive results in liver disease in general than was obtained by examining the urine. This opinion was also expressed by Bode,⁵⁶ Noah,⁵⁹ Jezler,⁶⁰ Kahler,⁶¹ and Davies.⁵⁴

Until recently, clinical studies of the blood sugar curve after galactose

ingestion were made without any attempt to determine separately the amount of galactose present. This explains the extremely variable results obtained and may also explain the frequently noted association of low blood sugar with increased urine galactose. In such cases it seemed probable that the blood glucose was lowered to such a degree that even after galactose feeding the total blood sugar remained low. Relying on the fact that galactose is much less easily fermented by yeast than is glucose, Somogyi⁶² devised methods for their separate determination. These may be used in the urine when the test is carried out in a diabetic and have been applied to the study of the blood by Bloch and Weisz,²⁰ and Petow, Kosterlitz and Naumann^{63,64}

Perhaps the most informative of the papers dealing in detail with the characteristics of the blood sugar curve after galactose feeding is that of Bloch and Weisz²⁰. They found that in normal individuals the rise in blood sugar frequently begins within five minutes after the galactose is taken. This is too soon for the galactose to have reached the blood, and Bloch and Weisz showed that this early rise is due to an increase in glucose, which is assumed to have been reflexly released from the liver. When the galactose reaches the blood stream fifteen or twenty minutes later there is slowing up of this release of glucose or some of the glucose actually may be reabsorbed so that the total blood sugar does not become very high. When there is parenchymal liver disease the release of glucose from the liver is unchecked and since the liver is also less able to hold the galactose, marked hyperglycemia is produced. If the hepatic disease is very severe, the liver may contain so little glycogen that no glucose is released. In such a case the total blood sugar will be quite low and, since there is no threshold for galactose, we have the appearance in the urine of an amount of sugar which seems entirely disproportionate to the degree of glycemia.

The reported studies of galactose tolerance by means of blood sugar determinations indicate that this method is more accurate in diagnosing liver disease in general, and particularly cirrhosis, than is a determination of galactosuria. It is important to note, however, that even in those papers which emphasize the value of the blood method the majority of cases of jaundice due to parenchymal liver damage show marked urinary excretion of the sugar. Indeed, Noah⁵⁹ and Elek and Oppenheimer⁵⁷ cite cases of catarrhal jaundice in which galactosuria was marked in the presence of a normal blood sugar curve. Since the blood method can hardly be said to be accurate unless a separate determination of galactose is done, a procedure rarely practicable in the average hospital, and since it offers no advantage over simple urine examination in determining the types of jaundice, we feel that there is little reason for its use for this purpose.

That pathological galactosuria can occur in patients who have no liver disease became known shortly after the introduction of this test. In 1911 and 1912 Pollitzer⁶⁵ reported patients who had marked disturbance of the vegetative nervous system and also one with hyperthyroidism whose tolerance to galactose was definitely decreased. These patients had normal

glucose tolerance Since then pathological galactosuria has been noted in hyperthyroidism,^{66, 44, 37} status lymphaticus,⁵² severe asthenia,⁶⁷ marked neuroses,^{44, 37} Addison's disease⁶⁸ and continued fever⁶⁹ That some neurological factor may be involved in the regulation of the blood and urine sugars after galactose feeding is suggested by the work of Hirschhorn, Pollak and Selinger⁷⁰ and of Pollak and Selinger⁷¹ It was reported by them that the administration of ergotamine and atropine lowered the blood sugar curve and reduced the galactosuria These workers felt that there is some neural or hormonal control of the liver cell activity in assimilating the sugar The drugs, by releasing this control, increased the liver's power to utilize the galactose Bauer and Wozasek⁷² confirmed this influence of ergotamine and atropine and felt that it indicated a sympathetic stimulation of the liver to assimilate this sugar It seems probable, therefore, that the ability of the liver to handle galactose is at least in part under the control of the vegetative nervous system That the endocrine glands also exert some effect on galactose tolerance seems true Rowe⁷³ has reported marked variability in tolerance for this sugar with endocrine disturbances Churchman⁷⁴ has found levulosuria in patients with functional hyperplasia of the posterior lobe of the pituitary We have seen patients with marked hypopituitarism whose tolerance for all sugars was increased and who were able to take tremendous doses of galactose, in one case up to 70 grams, without causing sugar to appear in the urine That these influences of the nervous system and endocrine glands limit somewhat the value of the test from a liver standpoint must be admitted While, however, the endocrine disturbances which elevate galactose tolerance might lessen the probability that coincident hepatic dysfunction would cause excessive galactosuria, they do not detract from the diagnostic value of this if it is found It must also be realized that those glandular conditions, and notably hyperthyroidism, which cause decreased galactose assimilation may do so because of secondary liver damage For these reasons, and because association of hepatic disease with endocrine or nervous disturbance is uncommon and should ordinarily be recognized, we do not feel that the value of galactosuria in the differential diagnosis of jaundice is greatly lessened

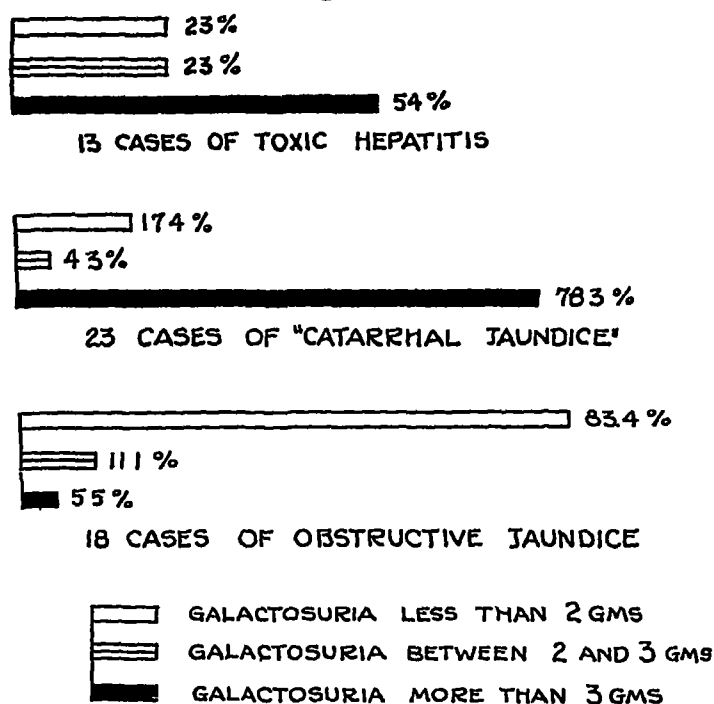
We will not enter into a detailed consideration of the clinical aspects of the levulose tolerance test The aid which it affords in the diagnosis of liver disease has recently been stressed by Kimball⁵ In the differentiation of the individual hepatic disorders, however, levulose is not of much value Hohlweg⁷⁵ noted marked decrease in tolerance to this sugar in experimental jaundice whether due to phosphorus poisoning or to ligation of the common duct Strauss⁷⁶ stated that the levulose test is positive in 70 to 75 per cent of cases of catarrhal and luetic jaundice and in 62.5 per cent of mechanical jaundice The difference in the incidence of positive results in these two types of icterus is not sufficient to be of much assistance in differentiating them

During the past two years we have used the galactose tolerance test in

studying 54 cases of jaundice. This group was composed of 18 patients with obstructive jaundice, 23 with catarrhal jaundice and 13 with toxic hepatitis. The results of these examinations are summarized in tables 1, 2, and 3 and in chart 1. Galactosuria of three grams or more occurred in 54

CHART I

Results of the Galactose Tolerance Test in 54 Cases of Jaundice. A 40 Gram Dose of the Sugar Was Used



per cent of the patients with toxic hepatitis, in 78.3 per cent of those with catarrhal jaundice and in only 5.5 per cent of those with jaundice due to obstruction. Although this series is comparatively small, these figures agree very closely with those of Worner,³⁸ whose results have already been mentioned.

Of the group with obstructive jaundice only one patient had a definitely positive response to the test. He excreted more than three grams of galactose on two occasions. This patient had a stricture of the common bile duct with jaundice of four weeks' duration. At operation definite biliary cirrhosis was found. Two other patients, however, also had biliary cirrhosis but excreted normal amounts of the sugar so that we do not feel that this alone is a cause of decreased galactose tolerance. Two patients with obstructive jaundice had galactosuria of between two and three grams. This might be considered suggestive of liver cell damage but in both of these cases the duration of the jaundice was short and nothing was found other than the slight increase in excretion of the sugar to indicate that such damage existed. There was no correlation between the degree of jaundice and the galactose passed in the urine. Most of the cases in this group had been jaundiced for a relatively short period. In one patient, however, who had a

TABLE I
Results of the Galactose Tolerance Test in Obstructive Jaundice

	Age and Sex	Duration of Jaundice	Galactose Excretion (Gm)	Serum Bilirubin (Mg %)	Cause of Obstruction
1 P M	58 ♂	4 weeks 5	5.24 3.09	9.0 15.0	Stricture of Common Duct (Biliary Cirrhosis)
2 J McB	56 ♀	5	0	8.0	Carcinoma Head of Pancreas
3 L G	26 ♀	8 " 10 "	1.85 0.9	8.0 6.4	Cholelithiasis
4 A D	58 ♀	12 days	0	14.0	Carcinoma of Gall-Bladder
5 T S	42 ♂	1 week	0.937	1.7	Chronic Pancreatitis
6 J K	69 ♂	4 weeks	1.065	36.0	Cholelithiasis Carcinoma Head of Pancreas
7 C S	48 ♀	2 days	1.404	1.5	Cholelithiasis (Biliary Cirrhosis)
8 I S	50 ♀	2 weeks	1.126	10.0	Cholelithiasis
9 A G	46 ♂	1 day	1.336	0.3	Cholelithiasis
10 M H	66 ♀	Unknown	1.776	0.9	Cholelithiasis Pancreatitis
11 C O'N	43 ♂	5 days	0	2.75	Cholelithiasis (Biliary Cirrhosis Pancreatitis Hepatic Abscesses)
12 T A	50 ♀	3 weeks	1.045	2.5	Cholelithiasis (Hepatitis)
13 W M	24 ♂	Unknown	1.73	0.7	Cholangitis
14 F K	57 ♂	12 days	2.53	8.0	Cholelithiasis
15 D T	18 ♀	6 "	1.64	6.0	Cholelithiasis
16 B J	52 ♀	19 "	0.336	0.75	Cholelithiasis
17 S II	55 ♀	About 5 months	0	1.8	Operative Injury to Common Duct
18 A J	57 ♂	18 days 103 "	2.09 0.25	16.5 12.0	Carcinoma of Pancreas and Liver

partial obstruction of the common duct for about four months the galactose tolerance was normal

Of the 23 patients with catarrhal jaundice only five excreted less than three grams of galactose and of these one patient passed 2.005 grams. The other 18 had galactosuria of more than three grams. Seven of the 13 patients with toxic hepatitis excreted more than three grams of the sugar, three of the remaining six passed between two and three grams of galactose

TABLE II
Results of the Galactose Tolerance Test in "Catarrhal Jaundice"

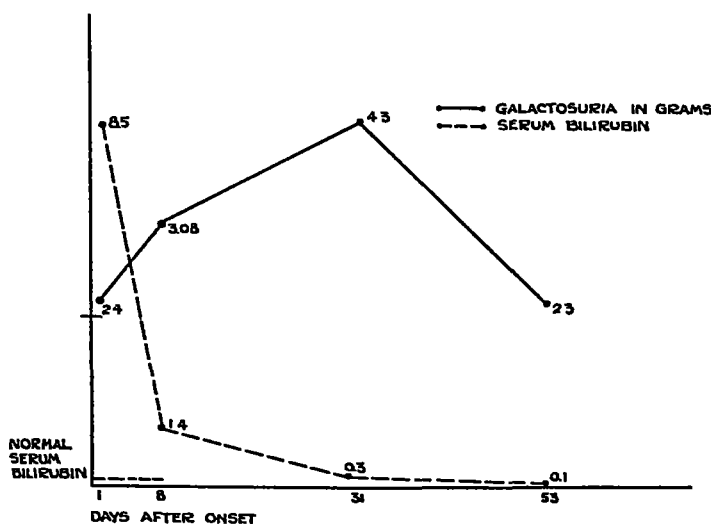
	Age and Sex	Duration of Jaundice (Days)	Galactose Excretion (Gm)	Serum Bilirubin (Mg %)	Wassermann Reaction
1 F M	27 ♂	9	5.125	6.0	Positive
2 L L	22 ♀	11 22	5.63 10.0	16.0 10.0	"
3 R G	27 ♀	11 19 36 69	4.55 4.32 4.799 2.079	15.0 3.9 0.4 0.35	Negative
4 T N	14 ♂	9 16 23	4.68 2.85 0	2.2 0.85 0.75	"
5 G K	14 ♂	9	18.08	4.0	"
6 C L	32 ♂	22	0.748	18.0	"
7 S H	50 ♀	36 52	3.95 2.29	2.0 1.6	"
8 J P	43 ♂	15 25 70	4.86 4.36 2.025	13.5 11.0 0.5	"
9 R D	29 ♀	11	2.005	6.0	"
10 E G	21 ♀	23	1.24	1.5	"
11 F R	18 ♂	8	11.0	3.0	"
12 A R	43 ♀	15 27	10.08 5.13	7.0 8	"
13 P M	37 ♀	5 49 94	3.08 6.51 4.7	2.4 0.6	"
14 D S	53 ♂	15	0.5	4.5	"
15 W H	31 ♂	7 13	14.95 2.56	7.0 5.0	"
16 I H	15 ♀	10	5.24	—	—
17 E F	31 ♂	11 32	3.35 0.288	— —	Negative
18 R D	29 ♀	9 29	12.011 2.855	6.0 —	Positive
19 E G	25 ♂	18 37	3.3 1.91	1.4 —	Negative
20 D M	13 ♀	6 18	3.38 2.71	2.0 0.75	"
21 E K	23 ♀	8 14	6.59 2.716	18.0 6.0	Positive
22 W M	55 ♂	15 19	6.92 2.32	13.0 7.0	Negative
23 S R	32 ♂	25	1.25	1.5	"

In the cases of toxic hepatitis and catarrhal jaundice there was extreme variability in the amount of galactose in the urine. This ranged from 0.147 to 18.08 grams. There was no relationship between the degree of jaundice and the galactosuria. The highest excretion, 18.08 grams (practically one-half of the sugar taken), occurred in a patient whose serum bilirubin was four milligrams per cent. The smallest amount of galactose was passed by a patient whose serum bilirubin was 12 milligrams per cent. The most severe jaundice was seen in a man who had galactosuria of only 1.017 grams. These findings emphasize the fact that the various liver functions can be separately disturbed, a point recently stressed by Cantalow.⁷⁷

Bauer²⁸ and also Wagner,³⁷ noted that in many cases of hepato-cellular jaundice the high galactose excretion frequently persisted when the serum bilirubin had returned to normal. We noted this in some of our patients, for instance, W. R. (Chart 2). This patient entered the hospital with

CHART II

The Relation between Serum Bilirubin and Galactosuria in W. R. Who Had Pneumonia and Jaundice



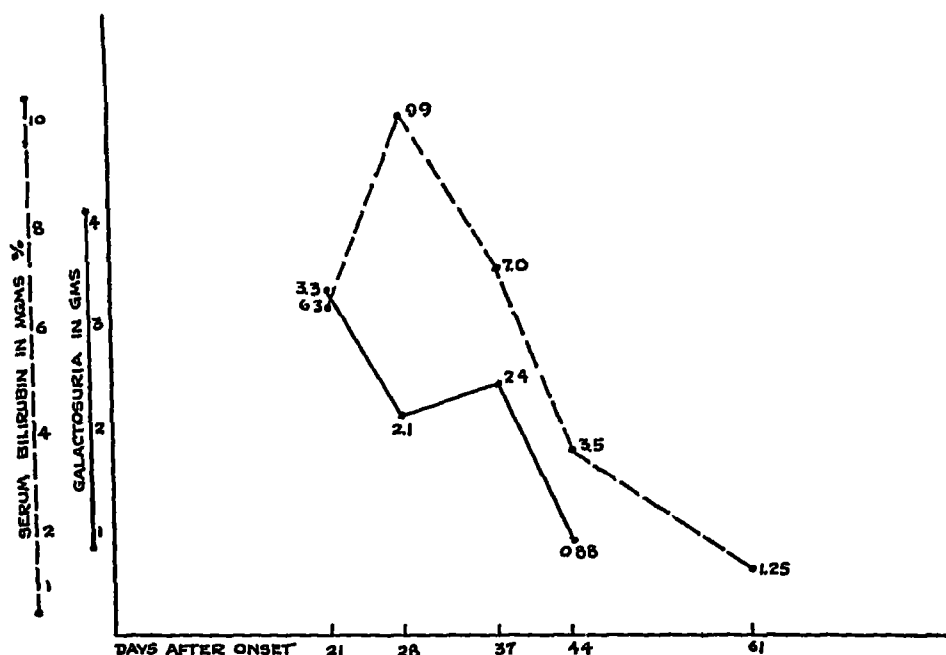
pneumonia and jaundice. Despite a rapid drop in the serum bilirubin the galactose tolerance decreased, but slowly, and at a time when the jaundice was entirely gone he still excreted 2.3 grams of the sugar. In another patient, however, the opposite picture was seen. This man, W. C. (chart 3), had arsenical hepatitis. His galactose excretion was never very high while under our observation and returned to normal rapidly. The jaundice, on the other hand actually increased and did not entirely disappear for months. These cases are further proof of the dissociation of the individual liver functions and of the necessity for using more than one test in studying this organ.

The duration of excessive galactosuria in the cases of toxic hepatitis and catarrhal jaundice was extremely variable. In some cases it was gone within three weeks. In others it persisted for very long periods, even as long as

three months. Certainly, normal liver function cannot be said to have been restored if the galactose excretion is high, even though other evidence of hepatic disease has disappeared.

CHART III

The Relation between Serum Bilirubin and Galactosuria in W C Who Had Arsenical Hepatitis



In our group with catarrhal jaundice four had positive Wassermann reactions. Neugebauer⁸⁴ reported that of 22 patients with early lues but no jaundice the galactose excretion was over three grams in 15. This high frequency of decreased galactose tolerance in syphilis uncomplicated by hepatic disease has not been noted by others. We believe that the incidence of syphilis is no higher in our group than in our hospital patients as a whole. We do not feel that the lues was a cause of the jaundice in these cases, although, as Ruge⁷⁸ states, it may have made the patients more susceptible to the particular agent that causes catarrhal jaundice.

In considering the results of the galactose tolerance test in our cases of catarrhal jaundice and toxic hepatitis we were interested in determining what relationship existed between the duration of the jaundice and the results of the test. Roubitschek²⁰ had noted that the galactosuria that is caused by phosphorus poisoning tends to decrease if the poisoning is prolonged. He ascribed this to regeneration of the liver and resumption of its ability to assimilate the sugar. Bloch and Weisz²⁰ also felt that with regeneration the liver tissue regained its power to form glycogen from galactose. Althausen⁷⁹ states that the newly formed liver cells can readily maintain the carbohydrate regulating function. Other workers⁸⁰ have concluded that a high galactose excretion is always obtained in patients with diffuse liver cell damage unless the test is delayed sufficiently to permit liver regeneration.

TABLE III
Results of the Galactose Tolerance Test in Toxic Hepatitis

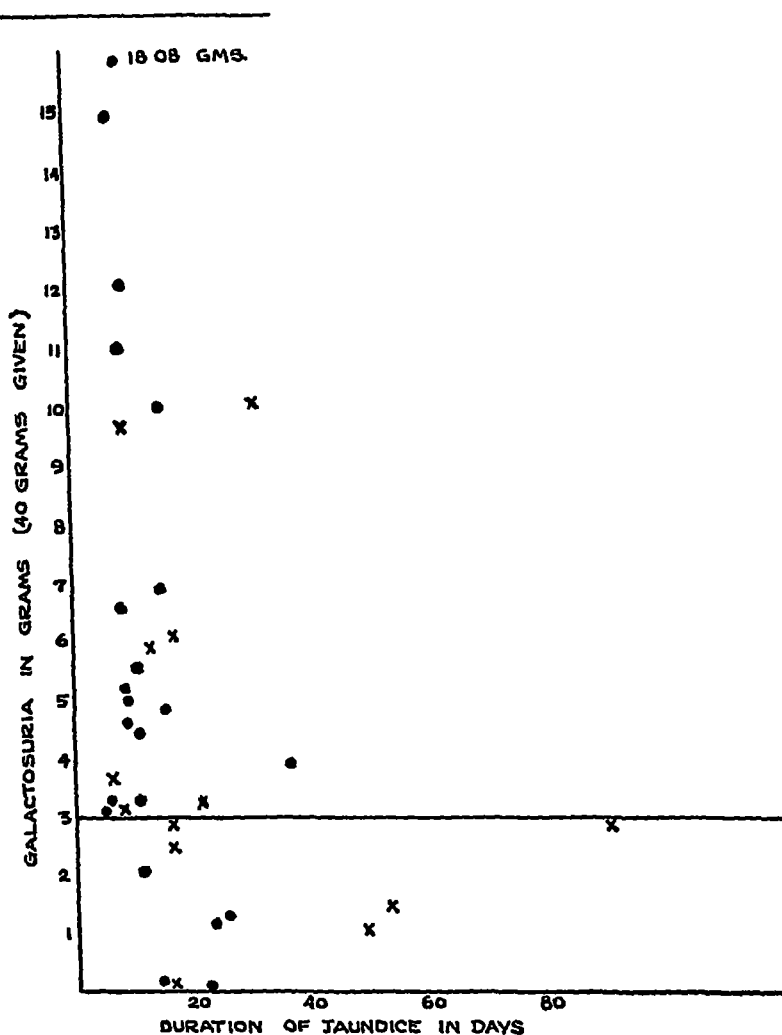
	Age and Sex	Duration of Jaundice (Days)	Galactose Excretion (Gm)	Serum Bilirubin (Mg %)	Toxic Agent
1 D S	20 ♂	16 31	2.845 2.865	4.8 0.9	Arsphenamine
2 E M	20 ♂	6 12 19	3.72 8.86 5.32	8.0 7.0 4.0	"
3 W C	37 ♂	21 28 37 44	3.296 2.102 2.4 0.88	6.3 9.9 7.0 3.5	"
4 G S	31 ♂	13 26	5.85 3.48	0.7 0.4	"
5 M W	47 ♀	16	2.582	10.5	"
6 S B	44 ♀	53	1.47	7.0	"
7 M B	49 ♀	16	0.147	12.0	"
8 S S	35 ♂	49	1.017	22.0	"
9 M P	64 ♀	17 20 24	6.08 2.8 1.74	— — 2.0	Cinchophen
10 R L	26 ♀	31	10.5	15.0	Cinchophen and Cholecystography
11 J C	57 ♀	9 22	9.742 3.29	3.0 —	Cinchophen
12 W R	31 ♂	1 8 31 53	2.38 3.08 4.3 2.3	8.5 1.4 0.3 <0.2	Pneumonia
13 V DeL	29 ♀	90	2.9	—	Toxemia of Pregnancy Ending in Acute Yellow Atrophy

In our 13 cases with toxic hepatitis a definitely positive result, an excretion of three grams or more, occurred in patients who had been jaundiced from six to 31 days (average 10.7 days). Definitely negative results, excretion of less than two grams, were found in patients who had been jaundiced from 16 to 53 days (average 39.3 days). If the cases with a doubtfully positive response, that is, with an excretion of between two and three grams, are included with those definitely positive, the average duration of the jaundice at the time of the galactose test becomes 22 days.

Of the 23 cases with catarrhal jaundice 18 had a galactosuria of three grams or more. The duration of jaundice in these patients varied from five to 36 days (average 11.7 days). The duration of jaundice in the five cases which excreted less than three grams ranged from 11 to 25 days (average 19.1 days). These findings are presented in chart 4.

CHART IV

The Degree of Galactosuria in Relation to the Duration of the Jaundice in 13 Cases of Toxic Hepatitis (x) and 23 Cases of "Catarrhal Jaundice" (•)



Although in both these groups the negative results were obtained in patients whose jaundice was of a longer average duration, the duration of the individual cases varied sufficiently to warrant further analysis. Since the pathogenesis of the jaundice is known in those who had toxic hepatitis, these cases will be considered separately. In this group the three negative results were obtained in patients who were first seen when the jaundice had been present for 16, 49, and 53 days. At first glance it would seem that in the last two cases the long continuance of the disease had permitted regeneration of the liver tissue and that this had restored the normal liver function. This thought, however, is not substantiated by the clinical course of these patients. One died, probably of acute yellow atrophy, the day after the galactose test was done. The other patient, a man with arsenical hepatitis, developed subacute liver atrophy with marked increase in the jaundice and tyrosin in the urine. The galactose test remained repeatedly negative. It is possible, of course, that in both of these patients sufficient functioning

hepatic tissue remained to normally assimilate the galactose. The important point is, however, that very severe liver damage can exist and the galactose test still give a normal result.

In patients with catarrhal jaundice the disease was also of longer average duration in those whose galactose test was negative. In this illness, however, the overlapping of the durations of the jaundice at the time of the positive or negative results was even more marked than in the group with toxic hepatitis. It was also noted that in some of the patients high degrees of galactosuria persisted over long periods. These facts led us to believe that duration of the disease may not be the only factor in a case of catarrhal jaundice which determines whether the galactose test shall be positive or negative.

Catarrhal jaundice is not a disease entity*. It is probable that the symptom complex that goes by this name includes cases of jaundice of varied etiology and pathogenesis. The early conception of the presence of cholangitis or duodenitis in every case has been disproved. When Bauer noted that excessive galactosuria occurred in so many of the patients with this type of jaundice he concluded that the essential defect was disease of the liver cells themselves. There are cases, however, in which the galactose tolerance test is negative, even when done early in the illness. It has been thought by Adler and Jeddeloh⁸¹ that this variation in galactosuria indicates that there are two types of catarrhal jaundice, one due to liver cell damage and one due to actual catarrh of the bile ducts. Bockus and Tumen,⁸² in a study of their cases of catarrhal jaundice, compared the patients with excessive galactose excretion with those in whom this was normal. They found that in the cases with positive response to the test, splenic and hepatic enlargement were more frequent and that the jaundice seemed to run a more prolonged course. The patients in whom the test was negative showed a higher incidence of biliary obstruction and catarrh. It was not felt "that the difference in the incidence of these findings was sufficient to warrant the conclusion that the galactose test in itself separates one type of so-called catarrhal jaundice from another." It does seem probable, though, that a positive galactose test in a case of catarrhal jaundice indicates that the icterus is due to actual disease of the liver cells themselves, that is, to hepatitis. When, on the other hand, the test is negative, especially early in the course of the illness, this fact suggests that the jaundice is due to obstruction in the ducts from inflammatory changes.

The results of our use of the galactose tolerance test in patients with icterus agree in general with those of Bauer and of Worner. We have noted that in obstructive jaundice the test is practically always negative. On the other hand, positive results are obtained in those types of jaundice of which hepato-cellular damage is the cause. The majority of cases of toxic hepatitis and catarrhal jaundice show increased galactosuria. Negative re-

* Throughout this paper we have used the term catarrhal jaundice not because we feel that it represents a disease entity but because it is convenient to so designate a group of conditions at present not well differentiated.

sults to the test, however, may be obtained in undoubted cases of hepato-cellular damage, even when this is of the utmost severity. In catarrhal jaundice a negative result to the galactose tolerance test may be obtained for one of two reasons. The test may have failed to show the presence of hepatitis or the jaundice may have resulted from obstructive biliary catarrh. This last possibility is particularly suggested by the occurrence of normal galactosuria in association with a spleen of normal size and evidence by duodenal drainage of biliary obstruction.

We feel that a positive galactose tolerance test in jaundice is almost pathognomonic of hepato-cellular damage. If the test is negative, this condition is not ruled out, particularly if the test is carried out late in the course of the illness.

We wish to express our gratitude to Dr. H. L. Bockus for kindly permitting us to use the records of many of his cases in preparing this paper.

REFERENCES

1. BLANKENHORN, M. A. Clinical significance of jaundice, Jr. Am. Med. Assoc., 1930, xcv, 1066-1068—A simple test to differentiate between obstructive and other types of jaundice, *ibid.*, 1931, xcvi, 459-460.
2. ALTHAUSEN, T. L., and MANCKE, R. Kombinierte Leberfunktionsprüfung, *Deutsch. Arch. f. klin. Med.*, 1931, clxx, 294-301.
3. SACHS, H. Über die Bedeutung der Leber für die Verwertung der verschiedenen Zuckerarten im Organismus, *Ztschr. f. klin. Med.*, 1899, xxxviii, 87-126.
4. STRAUSS, H. Zur Funktionsprüfung der Leber, *Deutsch. med. Wchnschr.*, 1901, xxvii, 757-759, 786-787.
5. KIMBALL, S. Levulose tolerance test, study of its value with special reference to mild and chronic diseases of liver, *Guy's Hosp. Rep.*, 1932, lxxxii, 157-255.
6. BAUER, R. Weitere Untersuchungen über alimentäre Galaktosurie, *Wien. med. Wchnschr.*, 1906, lvi, 2537-2545—Über die Assimilation von Galaktose und Milchzucker beim Gesunden und Kranken, *ibid.*, 20-23.
7. DRAUDT, L. Über die Verwertung von Laktose und Galaktose nach partieller Leberausschaltung (Ecksche Fistel), *Arch. f. exper. Path. u. Pharm.*, 1913, lxxii, 457-474.
8. FISCHLER, F. Physiologie und Pathologie der Leber nach ihrem heutigen Stande, 1925, J. Springer, Berlin.
9. BOLLMAN, J. L., POWER, M. H., and MANN, F. C. Relation of liver to metabolism of galactose, *Proc. Staff Meet., Mayo Clin.*, 1931, vi, 724-725.
10. MANN, F. C., and MAGATH, T. B. Studies on the physiology of the liver, *Arch. Int. Med.*, 1922, xxx, 73-84, 171-181.
11. WÖRNER, H. (Aussprache), *Verhandl. d. Deutsch. Gesellsch. f. inn. Med.*, 1922, xxxiv, 117-118.
12. FOSTER, G. L. Studies on carbohydrate metabolism, *Jr. Biol. Chem.*, 1923, lv, 291-301, 303-314.
13. BROCARD, quoted by NOAH, G. Beitrag zur Leberfunktionsprüfung mittels Kohlehydratbelastung unter besonderer Berücksichtigung der Galaktose und ihrer Einwirkung auf den Blutzuckerspiegel, *Ztschr. f. klin. Med.*, 1926, civ, 150-173.
14. ISAAC, S., and ADLER, E. Über sterische Umwandlung von Hexosen durch Organe und Zellen (Ein Beitrag zur Frage der sogenannten Stereokinasen), *Ztschr. f. physiol. Chem.*, 1921, cxv, 105-129.
15. ABDERHALDEN, quoted by NOAH, G. Beitrag zur Leberfunktionsprüfung mittels Kohlehydratbelastung unter besonderer Berücksichtigung der Galaktose und ihrer Einwirkung auf den Blutzuckerspiegel, *Ztschr. f. klin. Med.*, 1926, civ, 150-173.

- 16 HOFMEISTER, F Über Resorption und Assimilation der Nahrstoffe Fünfte Mittheilung
Über die Assimilationsgrenze der Zuckerarten, Arch f exper Path u Pharm, 1888,
xxv, 240-256
- 17 CORI, C F The rate of glycogen formation in the liver during absorption of fructose
and galactose, Proc Soc Exper Biol and Med, 1925-1926, xxiii, 459-461
- 18 FOLIN, O, and BERGLUND, H Transportation, retention and excretion of carbohydrates,
Jr Biol Chem, 1922, li, 213-273
- 19 HARDING, V J, and VAN NOSTRAND, F H Variations in blood and urinary sugar after
ingestion of galactose, Jr Biol Chem, 1930, lxxv, 765-778
- 20 BLOCH, J, and WEISZ, M Reflex- oder Resorptionshyperglykämie?, Ztschr f d ges
exper Med, 1930, lxi, 453-461
- 21 HALBERKANN, J, and KÄHLER, H Liver function tests, isolation and identification of
d-galactose excreted in urine, Ztschr f physiol Chem, 1926, cliv, 34-38
- 22 WIERZUCHOWSKI, M Intermediärer Kohlenhydratstoffwechsel, intravenöse Galaktoseas-
similation unter dem Einfluss der Hormone des Hungers und der Nahrungsfaktoren,
Biochem Ztschr, 1931, ccxxvii, 92-102
- 23 CORLEY, R C Factors in metabolism of lactose, disposal of intravenously administered
galactose in rabbit, Jr Biol Chem, 1927, lxxiv, 1-18
- 24 BASCH, F, and POLLAK, L Über das Verhalten korperfremder Zuckerarten unter
Insulinwirkung, über den Einfluss des Insulins auf die Assimilationsgrenze ver-
schiedener Zucker, Arch f exper Path u Pharm, 1927, cxv, 89-101
- 25 WELTMANN, O Über den Einfluss von Dextrose auf die Alimentäre Galaktosurie, Wien
klin Wchnschr, 1929, xli, 8-10
- 26 BLOCH, J, and WEISZ, M Erhöhung der Galaktosetoleranz bei Leberkranken durch
Kohlehydratzufuhr, Ztschr f klin Med, 1929, cxl, 71-87
- 27 ROE, J H, and SCHWARTZMAN, A S Galactose tolerance of normal and diabetic sub-
jects, and effect of insulin upon galactose metabolism, Jr Biol Chem, 1932, xcvi, 717-
735
- 28 BAUER, R Über alimentäre Galaktosurie bei Ikterus, Deutsch med Wchnschr, 1908,
xxxiv, 1505-1507
- 29 ROUBITSCHKE, R Alimentäre Galaktosurie bei experimenteller Phosphorvergiftung,
Deutsch Arch f klin Med, 1912, cviii, 225-255
- 30 BONDI, S, and KONIG, F Zur Kenntnis des Ikterus catarrhalis, Wien med Wchnschr,
1910, lx, 2617-2703
- 31 REISS, E, and JEHN, W Alimentäre Galaktosurie bei Leberkrankheiten, Deutsch Arch
f klin Med, 1912, cviii, 187-224
- 32 WÖRNER, H, and REISS, E Alimentäre Galaktosurie und Lavulosurie Deutsch med.
Wchnschr, 1914, xli, 907-910
- 33 HATIEGAN, J Über die klinische Verwertbarkeit der alimentären Galaktosurie bei Leber-
krankheiten, Wien klin Wchnschr, 1914, xxvii, 358-361
- 34 NEUGEBAUER, H Zur Pathogenese des Ikterus catarrhalis, Wien klin Wchnschr, 1912,
xxv, 514-521
- 35 SISSON, W R A clinical study of two hepatic functional tests (galactose and pheno-
tetrachlorophthalin), Arch Int Med, 1914, xiv, 804-826
- 36 MALIWA, E Bemerkungen zur Galaktosetoleranz, Med Klin, 1914, v, 762-764
- 37 WAGNER, F Klinische Untersuchungen über die Bedeutung der verschiedenen zucker-
proben für die Beurteilung der Leberfunktion, Ztschr f klin Med, 1914, lxx, 174-199
- 38 WÖRNER, H Die praktische Bedeutung der Galaktoseprobe, Med Klin, 1919, xv, 1142-
1143
- 39 ROUILLARD, J L'exploration des fonctions hépatiques Étude de quelques méthodes
récentes, Rev de med, 1928, xlv, 5-31
- 40 FREY, W Zur Diagnostik der Leberkrankheiten, Ztschr f klin Med, 1911, lxxii, 383-
435

- 41 JACOBY, H Zur Differentialdiagnose und Prognose der Leberinsuffizienz mittels Galaktose und Lavulose, *Deutsch med Wchnschr*, 1927, liii, 232
- 42 FALTITSCHKE, F, and KRASSO, H Über Galaktoseprobe und Chromodiagnostik für Leberfunktionsprüfung, *Wien klin Wchnschr*, 1927, xl, 386-389
- 43 BECKMANN, K Klinische Erfahrungen mit der Leberfunktionsprüfung durch Milce of rebelastung, *Ztschr f klin Med*, 1929, cx, 163-175
- 44 STRAUSS, H Über neurogene und thyreogene Galaktosurie, *Neurol Centralbl*, 1913, xxxii, 1281-1284
- 45 BLOCH, J Über die Charakteristik der glykämischen Reaktion nach oraler Galaktosezufuhr bei Leberparenchymschraden, *Ztschr f klin Med*, 1929, cxii, 37-42
- 46 SCHELLONG, F, in BRUGSCH, Schittenhelm, *Klinische Laboratoriums Technik*, 1928, Berlin
- 47 MEYER, S, and STERN, G Über den Galaktosestoffwechsel im Säuglings und Kleinkindesalter, *Arch f Kinderh*, 1920, lxxviii, 241-254
- 48 ROWE, A W The metabolism of galactose I The threshold of tolerance in normal adults, *Arch Int Med*, 1924, xxxiv, 388-401
- 49 HARDING, V J, and MOBERLEY, O Urinary galactose in men and women after ingestion of galactose, *Jr Biol Chem*, 1930, lxxxix, 535-545
- 50 HIROSE, M Über die alimentare Galaktosurie bei Leberkrankheiten und Neurosen, *Deutsch med Wchnschr*, 1912, xxxviii, 1414-1416
- 51 FIESSINGER, N, and THIEBAULT, F Les concentrations galactosuriques fractionnees comme methode d'exploration fonctionnelle du foie dans les ictères, *Bull et mem Soc méd d hôp de Paris*, 1931, lv, 1680-1682
- 52 BAUER, R Ikterus und Leberfunktion, *Wien Arch f inn Med*, 1923, vi, 9-36
- 53 BRUGSCH, H Hepatischer Ikterus, *Ztschr f klin Med*, 1931, cxviii, 435-463
- 54 DAVIES, D T Diagnosis of hepatic disorders, *Lancet*, 1927, i, 380-384
- 55 KAHLER, H, and MACHOLD, K Über das Verhalten des Blutzuckers nach Einnahme von Galaktose, *Wien klin Wchnschr*, 1922, xxxv, 414-417
- 56 BODE, O B Untersuchungen über die Bedeutung der Galaktoseprobe als Leberfunktionsprüfung, *Deutsch Arch f klin Med*, 1931, clxx, 165-175
- 57 ELEK, L, and OPPENHEIMER, A Beiträge zum Kohlehydrat-Stoffwechsel Leberkranker, *Wien klin Wchnschr*, 1927, xl, 246-248
- 58 BODANSKY, M Fructose, glucose and galactose tolerance in dogs, *Jr Biol Chem*, 1923, lvi, 387-393
- 59 NOAH, G Beitrag zur Leberfunktionsprüfung mittels Kohlehydratbelastung unter besonderer Berücksichtigung der Galaktose und ihrer Einwirkung auf den Blutzuckerspiegel, *Ztschr f klin Med*, 1926, civ, 150-173
- 60 JEZLER, A Beitrag zur funktionellen Leberdiagnostik, *Ztschr f klin Med*, 1929, cxl, 48-70
- 61 KAHLER, H Beiträge zur Leberfunktionsprüfung, *Med Klin*, 1925, xxi, 1295-1298
- 62 SOMOGYI, M Reducing non-sugars and true sugar in human blood, *Jr Biol Chem*, 1927, lxxv, 33-43
- 63 PETOW, H, KOSTERLITZ, H, and NAUMANN, H N Die Differenzierung des Gesamtblutzuckers nach Galaktosegabe in Glykose und Galaktose, *Klin Wchnschr*, 1930, ix, 1549-1550
- 64 KOSTERLITZ, H Untersuchungen über die Verwertung der Galaktose in physiologischen und pathologischen Zuständen, *Methodik, Ztschr f d ges exper Med*, 1932, lxxxii, 792-799
- 65 POLLITZER, H Über alimentare Galactosuria nervosen Ursprungs, *Wien klin Wchnschr*, 1911, xxiv, 1393-1396 — Über neurogene Galaktosetoleranz, *ibid* 1912, xxv, 1159-1162
- 66 BAUFER, R Die Prüfung der Leberfunktion mittels der Probe auf alimentare Galaktosurie, *Wien klin Wchnschr*, 1912, xxv, 939-941
- 67 UHLMANN, R Über Funktionsstörungen der Leber bei konstitutioneller Asthenie, *Arch f Verdauungs-Krankheiten*, 1915, xxi, 353-362

- 68 HOCHHEIM, W, and MISSKE, B Über den Wert der alimentaren Galaktosurie bei der Diagnose der Leberkrankheiten, *Deutsch Arch f klin Med*, 1931, clxxii, 511-522
- 59 REISS, E, and WÖRNER, H Neuere Untersuchungen über alimentare Galaktosurie bei Leberkrankheiten, *Verhandl d deutsch Gesellsch f inn Med*, 1922, xxxiv, 102-104
- 60 HIRSCHHORN, S, POLLAK, L, and SELINGER, A Über die Abgrenzung hepatozellulärer und neurohormonaler Galaktosurie durch den Ergotamin—Atropin—Versuch, *Wien klin Wchnschr*, 1930, xliii, 390-394
- 71 POLLAK, L, and SELINGER, A Über den Einfluss von Ergotamin und Atropin auf die Galaktoseassimilation bei Leberkranken und Lebergesunden, *Ztschr f klin Med*, 1931, ccvii, 476-499
- 72 BAUER, R, and WOZASEK, O Über den Einfluss von Ergotamin und Leberdiät auf die Leberfunktion, *Wien klin Wchnschr*, 1930, xliii, 1337-1341
- 73 ROWE, A W Sugar tolerance as aid to diagnosis, *Jr Am Med Assoc*, 1927, lxxix, 1403-1407
- 74 CHURCHMAN, J W The Strauss test for hepatic insufficiency, *Johns Hopkins Hosp Bull*, 1912, xliii, 10-15
- 75 HOHLWEG, H Zur funktionellen Leberdiagnostik, *Deutsch Arch f klin Med*, 1909, xcvi, 443-488
- 76 STRAUSS, H Zur Funktionsprüfung der Leber, *Deutsch med Wchnschr*, 1913, xxxix, 1780-1783
- 77 CANTAROW, A Van den Bergh reaction and bromsulphalein test in estimation of hepatic functional impairment, *Am Jr Med Sci*, 1932, clxxxiv, 228-240
- 78 RUGE, H Zehn Jahre Gelbsucht in der Marine (1919-1929), *Beobachtungen an 2500 Fällen (Statistik, Zusammenhänge mit Syphilis und Salvarsan, Klinik, Epidemiologie)*, *Ergebn d inn Med u Kinderh*, 1931, xli, 1-12
- 79 ALTHAUSEN, T L Functional aspects of regenerated hepatic tissue, *Arch Int Med*, 1931, xlviii, 667-675
- 80 SHAY, H, SCHLOSS, E M, and RODIS, I Galactose tolerance test in differential diagnosis of jaundice, *Arch Int Med*, 1931, xlvii, 650-659
- 81 ADLER, A, and ZU JEDDELOH, B Zur feineren Diagnostik der Leber- und Gallenwegserkrankungen, Bilirubin und seine Derivate in Blut, Harn und Stuhl Leberkranker, der mechanische Ikterus, *Deutsch Arch f klin Med*, 1929, cliiv, 129-146—Zur feineren Diagnostik von Leber- und Gallenwegserkrankungen, der Gallenfarbstoff und seine Derivate in Blut, Harn und Stuhl bei Leberkranken, der mechanische Ikterus, *ibid*, 282-297
- 82 BOCKUS, H L and TUMEN, H J *South Med Jr* (In press)

CONCERNING PLACENTAL HORMONES AND MENSTRUAL DISORDERS¹

By A. D. CAMPBELL, *Montreal, Canada*

CERTAIN placental extracts are now in common use in the treatment of disorders of menstruation. Following upon a not inconsiderable experience in 472 cases, it seems justifiable at this stage to discuss the theoretical basis for their use and also the results obtained by treatment. The first of these extracts is *Emmenin*, first defined by Collip (1930) as an alcohol-soluble, ether-insoluble extract of human placenta. In the light of recent work of Collip, Browne and Thomson (1932), it appears that *Emmenin* is probably a complex, containing as its active principle an ether-soluble trihydroxy-estrin, similar to the theelin of Thayer, Levin and Doisy (1931) and trihydroxy-estrin of Marrian (1930), but differing from them physiologically, as they in their turn differ from the theelin of Doisy (1929) or ketohydroxy-estrin of Butenandt (1929), in being relatively inert in the castrate animal, while preserving high activity in the immature animal with intact but prepubertal ovaries. Collip, Browne and Thomson (1932) therefore suggest that *Emmenin* is converted by the ovary, even the immature ovary, into some more active form of estrin, and this conception agrees well with clinical experience. It is interesting that Butenandt and Stormer (1932) find that their purest preparations of trihydroxy-estrin, free from all traces of ketohydroxy-estrin, have little activity in the castrate animal, their activity in the immature animal has not yet been reported.

The second of the preparations used is the anterior pituitary-like hormone extracted by Collip, Thomson, McPhail and Williamson (1930) from human placenta by means of acetone, and suitably purified. In contrast to *Emmenin*, it is insoluble in 85 per cent alcohol, and being destroyed by digestive enzymes, must be administered by injection. It is almost certainly identical with similarly purified extracts of human pregnancy urine, and the relation of these substances to the hormones of the anterior pituitary itself has been much clarified by the very recent work of Collip, Selye, Thomson and Williamson (1933). They have found that, while such anterior pituitary-like ("A P L") extracts of placenta or pregnancy urine do act directly upon the ovaries, they can only partially prevent the regression caused by hypophysectomy, that is, the pituitary itself contains, as well as a substance acting upon the ovary in the same sense as does A P L, an additional or complementary substance, not present in placenta or pregnancy urine. On the other hand, there is definite evidence that A P L has a stimulating action on the pituitary, probably indirectly, causing enlargement with signs of hyperactivity, and it is not unreasonable to suppose that

* Read before the American College of Physicians, Montreal February 7, 1933
From the Department of Obstetrics and Gynecology, McGill University

A P L causes a release of the required complementary substance from the pituitary. In any case, the action of the A P L in normal immature animals, as described by Collip, Thomson, McPhail and Williamson (1931), is to cause the ovaries precociously to assume normal adult size and structure, and to function, with the premature appearance of apparently normal estrus cycles, there is no action in castrated animals.

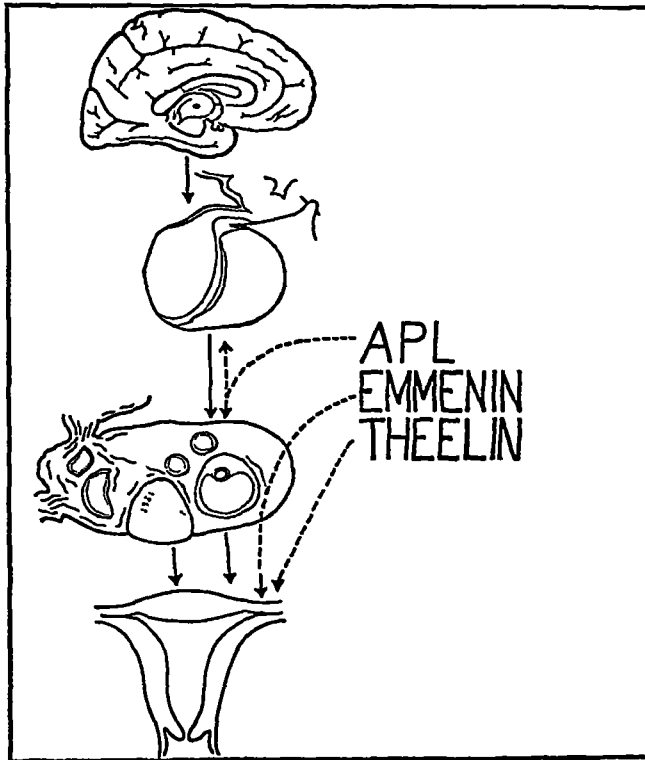


FIG 1 Schematic illustration of the action of certain placental hormones

Since there is some evidence of the presence of inhibitory substances in the pituitary (Collip) it is possible that alterations in this factor influence the function of the glands of internal secretion as revealed in ovarian dysfunction. Moreover, while certain centers in the hypothalamus undoubtedly influence the hypophysis, in order to clarify this most important point we must wait patiently for more experimental data.

These extracts have been employed in the treatment of disorders of menstruation of various kinds, but only in selected cases regarded as suitable for such treatment. Thus all cases in which pelvic lesions or abnormalities exist have been set aside, and are not further considered in this article. Moreover, it is known from animal experiments that disorders of the reproductive system may be due to the use of dietaries deficient in protein, in calcium, or in certain vitamins, and observations in Central Europe during the war justify the assumption that many present-day dietary fads and foibles contribute in a large measure to disorders of menstruation particularly in

adolescence In such cases, endocrine therapy, though not necessarily ineffective, does not appear to be entirely rational The remaining cases may be clinically divided into those showing disorders of the menstrual flow, either in interval, duration or amplitude, and those showing disorders giving rise to pain, which in turn may be premenstrual, menstrual or intermenstrual

Throughout this study the guiding principle has been kept in mind that menstruation is only the last, external manifestation of a long chain of physiological reactions In considering the disorders of menstruation, it must be remembered that, while the macroscopic and microscopic structure of the uterus is in itself significant, this structure is under the control of the hormones of the ovary (estrim and the hormone or hormones of the corpus luteum) The formation of these hormones is in turn controlled by the internal secretions of the anterior pituitary which similarly regulates the thyroid and the adrenal cortex and in its turn is no doubt to some degree regulated by the brain and the sympathetic nervous system These links, moreover, do not lead in one direction only The hormones of the ovary do undoubtedly influence the activity of the anterior pituitary, and the rhythm of the menstrual cycle is not improbably due to an interaction between these two organs Moreover, the effect of certain hormones of the ovary upon the anterior lobe of the pituitary gland may affect its influence upon other endocrine glands, and these may similarly affect the ovaries indirectly That the higher links in the chain are not unaffected by events in the uterus is evident, for example, in the difference between pregnancy and pseudo-pregnancy in many animal species Disordered menstruation, then, may be but the outward and visible sign of a dislocation of any one of these links, this idea is to be carried in mind in the subsequent discussion of the various disorders considered

AMENORRHEA

With the exception of instances of congenital obstruction in the Mullerian tract, there is a span in the life of the human female through which menstruation takes place with periodicity, interrupted normally by pregnancy and lactation Apart from such physiological states, amenorrhea is dependent upon alteration of physiology in some link or links in the so-called endocrine chain, in which undoubtedly the pituitary is of paramount importance

It has been found convenient to classify cases of amenorrhea in the following manner

Primary Amenorrhea

- | | | |
|---|---|--|
| (According to physical characteristics) | { | <ol style="list-style-type: none"> 1 With prepubertal characteristics 2 With normal post-pubeital characteristics 3 With abnormal pre- or post-pubertal characteristics <p>(Endocrinopathies)</p> |
|---|---|--|

Secondary Amenorrhea

(According to menstrual histories)	$\left\{ \begin{array}{l} 1 \text{ Oligomenorrhea} \\ 2 \text{ Oligomenorrhea with lapses} \\ 3 \text{ Regular menstruation with lapses} \end{array} \right.$
------------------------------------	---

In the prepubertal type of primary amenorrhea, the stature may be within normal limits, but the secondary sexual characters are largely absent axillary and pubic hair are developed at most to the degree of lanugo, the vaginal canal is small and frequently shows senile changes in the mucosa, the uterus is distinctly infantile. In such cases the ovaries, if they are developed at all, may be regarded as functionless, these individuals are physiologically or idiopathically prepubertal castrates. Absence of the sex element of the pituitary, without disturbance of the growth-promoting and other functions of that organ, would go far to explain such entities.

Somewhat similar in origin are the cases in which stature and sexual characters are normal, but in which menstruation has never occurred, the occasional occurrence of one or two periods of uterine bleeding simulating, but probably not exactly corresponding to, menstruation may be disregarded. Here again it is often tempting to suppose that the gonad-stimulating activity of the anterior pituitary has ceased, not, however, at so early a stage as in the preceding group, so that the secondary sexual characters have developed normally to a considerable degree. It is, on the whole, improbable that inflammation of the genitalia, or of the ovaries in particular, is an important cause of amenorrhea, since known cases of pelvic inflammatory disease rarely display amenorrhea in their subsequent course, and moreover it is certain that the amount of ovarian tissue normally present is greatly in excess of the amount required for the normal menstruation. For this and other reasons it seems more probable that the pituitary gland is primarily at fault. It is moreover quite unsafe to dismiss this possibility in cases where the sella turcica appears normal in the roentgen-ray, Cushing lends his authoritative support to the view that the gross size of the gland is no index of the degree of its activity.

The underlying cause of disturbed function is often obscure but in many instances is traceable to some toxic condition or febrile state in childhood or adolescence frequently escaping the attention or memory of patient or parent, even in adult life the pituitary is susceptible to toxic influences including those of the puerperal state. The association of amenorrhea with tuberculosis is a time-honored observation, but in addition the disorder not infrequently follows scarlet fever, diphtheria or influenza, refractory amenorrhea and diabetes are frequently associated. Over 75 per cent of cases of amenorrhea are directly traceable to some of the conditions above mentioned.

First among the cases which show amenorrhea in the presence of abnormal postpubertal characteristics may be placed the cases of so-called Simmonds' disease, in which all the functions of the pituitary are depressed. As Calder has recently pointed out, the condition parallels that of the hypo-

long-lived, or both. This view is supported by Mazer's finding of an enlarged corpus luteum in a case with decidua-like progestational endometrium and by the fact regularly observed that the cycles in cases of dysmenorrhea are usually prolonged to 29 or 31 days. Beckwith Whitehouse suggested that treatment should be directed to curtailing this prolonged life of the corpus luteum, which in turn probably depends on some disturbance of the endocrine balance between ovary and pituitary. At the present time our knowledge of this balance does not suggest any means of readjusting it in the desired sense, but an alternative method of treatment does suggest itself. It is known from the animal experiments of Reynolds and Allen, and others, that estrin inhibits the action of corpus luteum hormones in inducing progestational changes in the endometrium. If these latter are responsible for dysmenorrhea, it is not illogical to attempt treatment by the administration of substances actually or (as in the case of Emmenin) virtually of the estrin type. In fact, the results of Emmenin treatment in such cases appear to go beyond expectation in this respect. The administration of Emmenin reduces the length of the cycles to 28 days, the uterus becoming less hard and increasing in size. Treatment should be carried through three cycles (since it is commonly found that every second cycle is less severe) and the dose then gradually reduced, only in a few cases should recurrences be anticipated. Failures should be reviewed in the light of a more searching history and investigation. Dysmenorrhea occurs commonly in patients of a definite physical type, rarely in the obese or plethoric, the typical case is ultra-feminine, active mentally and physically, weighing 95 to 115 pounds, and with slightly raised basal metabolic rate, the uterus is small, anteflexed and hard.

Pain occurring simultaneously with menstruation (menorrhagia) is of a different nature. It occurs, as a rule, not in adolescence, but in adult life. There is usually, if not always, a lesion in the pelvic organs, real if not apparent, the cycles are frequently short and profuse, a large proportion of the cases are married, and sterility is an accompanying symptom. Intra-uterine investigation will very frequently reveal the presence of a polyp or small mural fibroid, which not only stimulates the uterus to violent contractions but may cause regurgitation within the pelvic cavity through the Fallopian tubes, giving rise to intense peritoneal irritation. Endometriosis within the abdominal cavity gives rise to symptoms so similar that differentiation is exceedingly difficult, it is not impossible that this condition has existed undetected in some patients who have failed to respond to Emmenin.

Intermenstrual pain, or "Mittelschmerz," presents an almost unanswerable problem. It is characterized by the onset of sharp pain 12 to 14 days before the expected period, and the pain frequently continues with acute exacerbations until a few hours before the onset of the menstrual flow, the cycles are usually regular. The symptoms are so suggestive of chronic appendicitis that laparotomy is usually performed on these patients sooner or later, in spite of these exceptional opportunities for investigation almost

no convincing information bearing on the cause of the condition has been obtained. Unilateral oophorectomy has frequently been performed, and it is found that thereafter pain does not recur on the operated side, this fact, together with the coincidence of the onset of pain with the alleged time of ovulation, suggests that the ovaries rather than the uterus are the seat of the pain. Yet since the pain is normally bilateral the relation to ovulation cannot be insisted on too heavily, though it is probable that even the ovary in which ovulation is not occurring at any one cycle shares with the other in certain disturbances such as hyperemia and congestion. Neither Emmenin nor A P L, nor, it would appear, any other form of endocrine therapy yet employed, has proved of any efficacy in this condition. Roentgen-rays have been employed by us in the treatment of intermenstrual pain. Following an artificial menopause of upwards of three months, menstrual epochs were unaccompanied by pain. The series is not large and sufficient time has not elapsed to speak with finality, yet our results seem to justify the consideration of such an heroic procedure in the treatment of "Mittelschmerz."

It should be emphasized that Emmenin therapy is essentially safe. In a group of 10 cases, Emmenin was administered daily (except during the periods) for several months without disturbing the normal menstrual cycles. If, however, administration was continued through the epoch, irregular prolongation of the flow or incomplete cessation was observed. No untoward effects, apart from occasional slight vertigo, headache, or nausea, in isolated cases were noted, three patients developed urticaria. No changes were observed in blood pressure levels, in some cases an initially high basal metabolic rate underwent slight reduction. The administration of Emmenin does not prevent impregnation nor interfere with gestation. Some 17 cases regarded as sterile became pregnant when treated for various menstrual disorders, the explanation is probably to be sought in the improved condition of the endometrium, or possibly in alteration of the vaginal reaction.

It may be of interest to review the possible cases of sterility attributable to the female, and the outlook for endocrine therapy in each type. Firstly, sterility may be due to failure of the ovaries to liberate viable ova, in some such cases, stimulation of the ovaries by anterior pituitary-like hormones might have a correcting influence, for example, in prevention of atresia of the follicle. Secondly, the ova liberated may fail to reach the uterus, whether because of some mechanical obstruction or because of derangement of the ciliary transporting mechanism, the latter type is that associated with endometriosis and ectopic pregnancies, and it is not inconceivable that it might be influenced by ovarian hormones. Thirdly, it is theoretically possible that the ovum and the sperm cannot unite to reproduce a viable embryo (for example, owing to association of lethal genes), such cases, if they exist, are doubtless refractory to all treatment. Fourthly, the uterus and vagina may be so abnormal—for example in the reaction of their secretions or the reactivity of their surfaces—that they are inhospitable either to the spermatozoa (so that intercourse could be fertile only at a very restricted period in

each cycle) or to the fertilized ovum (so that nidation fails or the embryo sooner or later loses its connection with the maternal tissues) Nearly all cases in this group could probably be influenced favorably by a correct supply of the hormones of the ovary, either introduced exogenously or evoked by stimulation of the ovary with appropriate extracts of the pituitary type

It has already been indicated that the influence of the pituitary upon the ovaries is a reciprocal one, this is nowhere more evident than when ovarian function ceases, for example as a result of castration Nevertheless, the origin of the various symptoms of the menopausal complex remains wholly obscure, and the treatment of the condition with placental hormones is a successful experiment without clear theoretical basis The symptoms may include alteration in blood pressure and in metabolic rate, with irritability in addition to flashes (*bouffées de chaleur*) frequently appearing before the actual cessation of menstruation, that is to say, in the presence of some degree of ovarian function They may persist long after apparent function has ceased It is a striking fact that so-called "idiopathic" amenorrhea before the climacteric infrequently leads, as does castration at a similar age, to the production of menopausal symptoms Emmenin has proved itself efficacious in the treatment of the menopausal syndrome of a milder form, provided that the symptoms have only recently appeared, the more general and more logical therapy is the A P L extract, which has been employed with signal success in cases with intact ovaries

The exhaustion of the potential follicles in such cases can be disproved histologically, but the fundamental alteration is possibly in the anterior pituitary gland Further support of this thesis lies in the fact that with the administration of A P L to such cases, the symptoms disappear in many instances, even if a considerable period has elapsed since the apparent termination of menstrual life, but since laboratory experiments and clinical trials have conclusively shown that the active principle employed is ineffective in the ovariectomized organism, the symptom complex of the so-called menopause is therefore apparently the result of deficient activity of both glands This is further borne out by the fact that post-menopausal patients when treated with A P L do not respond with menstruation, as do cases in mid-life with a corresponding period of amenorrhea Moreover, the disturbance disappears even in certain cases with similar symptoms resulting from irradiation These observations suggest that active graafian follicles and corpora lutea are not essential for the entire endocrine function of the ovary

Possibly the most striking application of A P L has been in the treatment of excessive uterine hemorrhage A preliminary report on the effect of such treatment was presented by us before the British Medical Association, August 1930 A classification of the various types of this disorder has been already offered (Campbell, 1931), here again, as in the classification of secondary amenorrhea, the type encountered influences the outlook for therapy

TABLE I
Varieties of Abnormal Uterine Hemorrhage

Group	Length of Cycle	Amplitude of Flow	Duration of Flow
A	Normal	Excessive	Normal
B	Normal	Excessive	Prolonged
C	Normal	Excessive	Normal, superimposed on constant bleeding background
D	Short (19-24)	Normal or excessive	Normal or prolonged
E	Short (14 days)	Normal	Irregular
F	Acyclic intermittent bleeding	Irregular	Irregular
G	Continuous excessive hemorrhages	—	—

The last group (G) may be further subdivided into four categories, according to the mode of development of the continued bleeding which may arise

- (a) By confluence of regular cycles of varying length of interval, with unduly prolonged duration of the flow
- (b) By confluence of irregular periods of metrorrhagia
- (c) Spontaneously, either after a normal menstrual cycle or more commonly after a period of amenorrhea
- (d) As an outcome of puberty

The first five types (A-E) are grouped as menorrhagia, and distinguished from metrorrhagia, in which all sign of regular cycles has been lost, the hemorrhage is irregularly intermittent (type F) or continuous (type G). The metrorrhagia cases are further subdivided according to the history of the onset of the condition, especially, the cases in which metrorrhagia has arisen at puberty and continued steadily thereafter form a distinct subgroup. Too much stress cannot be laid on the need for careful exploration of the cavity of the uterus in all cases, in order to determine the character of the surface of the wall, as well as to obtain samples of endometrium for histological study. There is no cancer age.

It is considered that the primary defect lies in pituitary function and that the more or less typical picture in the ovary is a reflection of this altered function. The researches of Schroeder and of Shaw have associated metrorrhagia with the presence of an ovary containing no active corpora lutea but marked by large cystic follicles, a histological picture suggesting an excess of estrin formation over the formation of the luteal hormone or hormones. This idea finds confirmation in certain experimental studies of the effects of estrin administration. It would therefore seem that the aim of therapy should be either to supply luteal hormones or to cause the ovary to form them, the latter being at present the more feasible procedure. But whereas most of those workers who have striven to do this have used extracts which produce a pathological degree of luteinization in experimental animals, and which apparently—to judge by the case histories reported—have a similar

action in the treated patients, the object of A P L treatment is to restore to the ovary a properly balanced structure and function. That this is not a vain hope is indicated firstly by the results of animal experiments, which show that, while A P L stimulates the ovary, it does not produce excessive luteinization save in enormous doses, far in excess of those which can be employed clinically. Secondly, and more important, it should be noted that in the majority of the successful cases of whatever type, the end result is the reestablishment of cycles normal in length and in duration and amplitude of flow. Only in the subgroup of metrorrhagias arising from *liberty* has a tendency for lapses of up to four menstrual cycles (possibly *attributable* to excessive luteinization) made its appearance. On the other hand *such* cases may thus be presenting transient irregular menstrual cycles not infrequently observed in adolescence. A P L has been used in a large number of cases of all types referred to earlier in the text, the response has been particularly gratifying.

While the true nature of *endometriosis* is not understood, there is reason to believe that deranged endocrine function permits the uterine mucosa to grow in a foreign locality. One patient with vaginal endometrial transplants was treated with A P L. The "rests" disappeared within six weeks. While such a result might have been fortuitous, it is considered worthy of reporting.

In nearly all of the cases in which success has been only partial or in which complete failure has been recorded, a more thorough examination has revealed the presence of some complicating factor obviously inaccessible to therapy of this type, such as the presence of an intra-uterine or adnexal lesion. Furthermore, it is essential that the ovaries contain potential follicles in order to correct so-called idiopathic uterine bleeding. It is therefore fitting to conclude with a repetition of the caution expressed at the beginning of this paper, that the first step in the introduction of endocrine treatment in any type of menstrual disorder is an accurate diagnosis, and the exclusion of cases in which structural abnormalities, neoplastic development or ineffective processes present an obstacle which no endocrine therapy can, or should be expected to overcome.

The extracts used in these studies were prepared in the Bio-Chemical Laboratory of McGill University by Prof. J. B. Collip. The method of preparation and physiological properties of these hormones have been published previously.

I wish to thank the staffs of the Royal Victoria Hospital and the Montreal General Hospital for their kind cooperation.

REFERENCES

- BUTENANDT, A. *Naturwissenschaften*, 1929, xvii, 879.
 BUTENANDT, A., and STORMER, I. *Über isomere Follikelhormone, Untersuchungen über das weibliche Sexualhormon*, *Ztschr. f. physiol. Chem.*, 1932, ccviii, 129-148.
 CALDER, R. M. Anterior pituitary insufficiency (Simmonds' disease), *Bull. Johns Hopkins Hosp.*, 1932, i, 87-114.
 CAMPBELL, A. D., and COLLIP, J. B. Notes on clinical use of certain placental extracts, *Canad. Med. Assoc. J.*, 1930, xxiii, 633-636.

- CAMPBELL, A D, and COLLIP, J B On clinical use of ovary-stimulating hormone of placenta, preliminary report, *Canad Med Assoc Jr*, 1930, xxii, 219-220
- CAMPBELL, A D, and COLLIP, J B Further clinical studies on anterior pituitary-like hormone of human placenta, *Canad Med Assoc Jr*, 1931, xxv, 9-19
- CAMPBELL, A D Further studies on anterior pituitary-like hormone, with special reference to irregular uterine bleeding, *Lancet*, 1932, ii, 561-565
- COLLIP, J B Sex hormones of female, review, *Canad Med Assoc Jr*, 1930, xxii, 212-214
- COLLIP, J B, THOMSON, D L, MCPHAIL, M K, and WILLIAMSON J E Anterior pituitary-like hormone of human placenta, *Canad Med Assoc Jr*, 1931, xxiv, 201-210
- COLLIP, J B, BROWNE, J S L, and THOMSON, D L Relation of emmenin to other estrogenic hormones, *Jr Biol Chem*, 1932, xcvi, pages xvii-xviii
- COLLIP, J B, SELYE, H, THOMSON, D L, and WILLIAMSON, J E Effect of prolonged administration of anterior pituitary-like hormone on pituitary and thyroid, *Proc Soc Exper Biol and Med*, 1933, xxx, 590-591 Replacement of gonadotropic action of pituitary in hypophysectomized rat, *ibid*, 665-667
- COLLIP, J B Interrelationship between the pituitary gland, the ovaries and the placenta, *Trans Royal Soc Canada, Section V*, 1932, i 137
- CUSHING, H Basophil adenomas of pituitary body and their clinical manifestations (pituitary basophilism), *Bull Johns Hopkins Hosp*, 1932, i, 137-195
- DOISY, E A, VELER, C D, and THAYER, S Folliculin from urine of pregnant women, *Am Jr Physiol*, 1929, xc, 329-330
- MARRIAN, G F Chemistry of estrin, improved method of preparation and isolation of active crystalline material, *Biochem Jr*, 1930, xxiv, 435-445
- MAZER, C, and GOLDSTEIN, L Clinical endocrinology of the female, 1932, W B Saunders Co, Philadelphia, p 227
- SCHRODER, R Die Pathogenese der Meno- und besonders der Metrorrhagien, *Arch f Gynaek*, 1919, cx, 633-658
- SHAW, W Irregular uterine hemorrhage, *Jr Obst and Gynaec Brit Emp*, 1929, xxxvi, 1-69
- THAYER, S A, LEVIN, L, and DOISY, E A Characterization of theelol, *Jr Biol Chem*, 1931, xci, 655-665
- WHITEHOUSE, B Pathology and causation of dysmenorrhea, *Jr Obst and Gynaec Brit Emp*, 1926, xxviii, 607-619

THE EFFECT OF VITAMINS AND THE INORGANIC ELEMENTS ON GROWTH AND RESISTANCE TO DISEASE IN CHILDREN¹

By ALAN BROWN, M D , F R C P (C), and FREDERICK F
TISDALL, M D , F R C P (C), *Toronto, Canada*

DURING RECENT years more and more attention is being devoted by the medical profession to the rôle of minerals and vitamins in human nutrition. In the present paper we wish to direct your attention to some of the work being done in this field at the Hospital for Sick Children, Toronto. This work has been undertaken not with the object of discovering methods for the cure of various disease conditions, but in an attempt to determine the value and importance of these dietary factors for normal development and resistance against disease.

There are at least 10 inorganic elements which are absolutely essential for life, viz, sodium, potassium, calcium, magnesium, phosphorus, chlorine, sulfur, iodine, iron and copper. From the standpoint of the practising physician, we are fortunate in having to watch the supply of only three of these elements, because any reasonable diet will furnish the other seven elements in adequate amounts. The supply of the three elements, calcium, iron and iodine, however, should not be left to chance.

Although calcium is the fourth most widely distributed element in the earth's crust, its occurrence in foods is quite limited. Our two chief sources of calcium are milk and leafy vegetables. From the standpoint of the child's diet, it may be stated that it is absolutely impossible to furnish an adequate amount of calcium unless liberal amounts of milk are included in the diet. This can be readily demonstrated by the following. A diet comparable to that found in many uninformed families composed of rolled oats, bread and butter for breakfast, beef, potatoes, carrots, cabbage and rice for dinner, potatoes, bread and butter and honey or jam for supper, with four ounces of fluid milk to go on the rolled oats and rice, supplies only 0.3 gram of calcium. Yet the average ten year old child requires approximately one gram of calcium each day (Rose). The additional 0.7 gram of calcium required can be furnished by one pint of milk, or a total milk intake of 24 ounces per day. If all the milk is omitted the amount of calcium furnished by the remaining portion of the diet is reduced to the absurdly low figure of 0.17 gram. It is thus evident that we depend largely on milk to supply the large calcium needs of the growing child.

Iron is another mineral element that is not so widely distributed in food that its supply can be left to chance (Sherman). This is particularly true in

* Presented in part before the British Medical Association, London, England, July 1932.
Read at the Montreal Meeting of the American College of Physicians, February 6, 1933.
From the Department of Paediatrics, University of Toronto, and the Hospital for Sick Children.

the case of the small infant, whose diet consists largely of milk and cereal, both of which foods are deficient in iron. Egg yolk, liver, spinach and other green vegetables are our richest sources of iron in foods.

From a series of experiments on rats we have found that with a lack of inorganic iron the rate of gain was reduced 33 per cent over a period of 11 weeks. The type of iron administered and also the presence of copper are essential in the diet, as proof of which a recent experiment was done in which a child with nutritional anemia was placed on a diet containing approximately 1.264 mg of iron daily. The hemoglobin was 5.5 grams per 100 c.c. of blood. Copper sulfate was given for a period of three weeks in daily doses of 2 mg. No change was noted in the hemoglobin. For the next two weeks organic iron was added in the form of hemoglobin crystals, so that the child was receiving the equivalent of 12 grains of iron daily. Again the hemoglobin level remained the same. The organic iron was replaced by inorganic iron in the form of ferrous chloride in a dose of 33 mg daily. The copper sulfate and the diet remained unchanged. In three weeks the hemoglobin had increased 2.4 grams per 100 c.c. of blood, and in another three weeks had reached the level of 11 grams of hemoglobin per 100 c.c. of blood, making a total increase of 5.5 grams of hemoglobin in six weeks. This demonstrates in the human what has been previously proved experimentally in the rat, namely, that copper, or copper and organic iron, are not efficient in hemoglobin regeneration.

With us, in the center of the North American continent, the iodine content of the water and the food is extremely low. We depend largely on iodized salt to furnish this element.

A lack of vitamin A in the diet results in a keratinization of the epithelial cells. Our chief supply of vitamin A is butter fat, egg yolk, carrots, spinach and cod-liver oil.

A lack of vitamin B₁ results in peripheral neuritis or beri-beri, while a lack of vitamin B₂ results in pellagra, and possibly certain skin diseases. Vitamins B₁ and B₂ are found largely in yeast, wheat germ, milk, liver, egg yolk, spinach and other leafy vegetables. Vitamin C, the anti-scorbutic vitamin, is found in oranges, lemons, tomatoes, cabbage and other fruits and vegetables. It is readily destroyed by heat in the presence of oxygen.

Vitamin D, the anti-rachitic vitamin, is not found in ordinary foods, with the exception of small amounts in egg yolk and summer milk. Fish oil, such as cod-liver oil, is our most concentrated natural source. In recent years vitamin D has been produced by the irradiation of ergosterol.

Vitamin E, the reproductive vitamin, is found in wheat germ, lettuce and other leafy foods.

In addition to the well recognized deficiency diseases produced by a lack of vitamins and minerals, we have studied the importance of these food elements to growth and resistance to infection. Each one of these vitamins and minerals is essential for life, so it is only reasonable to expect that if any one of them is omitted from the diet, the individual will eventually lose

weight and die In animal experiments this has been found to be the case In our rats fed a normal diet the average gain in weight over a period of six weeks was 100 grams When calcium was reduced from the optimal figure of 0.612 per cent to 0.260 per cent, the average gain over the same period was 80 grams In regard to phosphorus, we found that if this element was reduced from the optimal level of 0.450 per cent to 0.240 per cent, the animals, instead of making the normal gain of 100 grams in six weeks, gained only 66 grams With a lack of iron, the rate of gain was reduced 33 per cent over a period of 11 weeks

Some of the vitamins have been spoken of as the growth promoting vitamins, but a survey of figure 1 shows that a reduction of any one of the vitamins (with the exception of E) results in loss of weight

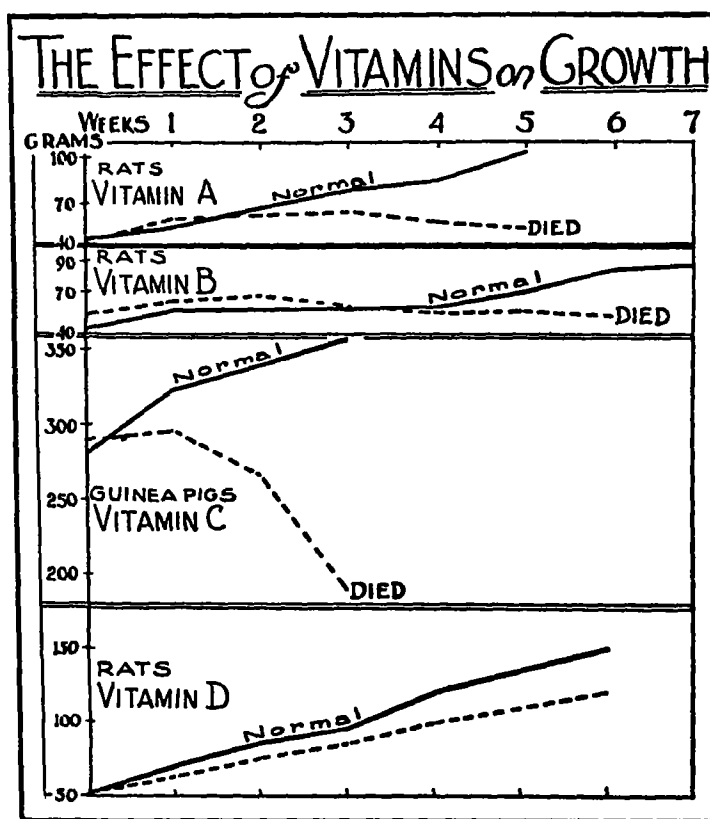


FIG 1 The effect of a lack of any one of the vitamins on growth

The influence of vitamin A in maintaining a normal condition of the epithelial cells of the respiratory tract and normal resistance against infection is so well recognized that this vitamin is frequently called the anti-infective vitamin By a method devised in our laboratories by Dr Elizabeth Chant Robertson, the effect of a lack of the vitamin B complex and of vitamin D has been studied to determine the procedure consisted of feeding the rat the desired deficient diet for a period of two to four weeks, and then giving by mouth a measured amount of an organism pathogenic for the rat, known as *Salmonella muritidis* The animals were then watched for a period of four

TABLE I

The Effect of the Vitamin B Complex on Resistance to Infection

Vitamin B Deficient Diet			Vitamin B Deficient Diet with 6% Dried Brewers' Yeast Added		
Total Number of Rats	Number of Survivors	Percentage of Survivors	Total Number of Rats	Number of Survivors	Percentage of Survivors
73	12	16%	68	47	69%

weeks, and the number of survivors noted. Blood cultures were made from the heart blood of all animals shortly after death, and the very occasional animal which did not show a positive culture was discarded as having died from some other cause. The results given in tables 1 and 2 show that a lack of the vitamin B complex and of vitamin D lowers the resistance of rats to infection.

TABLE II

The Effect of Vitamin D on Resistance to Infection

Rachitogenic Diet			Rachitogenic Diet with Addition of Vitamin D		
Total Number of Rats	Number of Survivors	Percentage of Survivors	Total Number of Rats	Number of Survivors	Percentage of Survivors
375	106	28%	364	201	55%

It has thus been shown that rachitic rats died in decidedly larger numbers after an oral infection with rat typhoid than similar controls fed vitamin D in addition to the rachitogenic diet. The following experiments were planned to test whether rachitic rats were also more susceptible to respiratory infections. As before, litters were divided, and half were put on a diet which caused rickets, and the other half were given the same diet with vitamin D (as 12½ per cent dried, vitamin D containing, bread) in addition. After 19 days on the diet the rats were all infected by six nasal instillations at daily intervals of a very heavy suspension of a *pasteurella bacillus*. Similar organisms cause pneumonia in rabbits, etc. Between the last two instillations a small amount of a dilute solution of brilliant green was dropped in the nose, as Bull had found that this increased the incidence of pneumonia.

All of the rats showed some nasal discharge after this treatment, but in the rachitic animals the discharge was more profuse and of longer duration. Three-quarters of the rachitic animals declined in weight after the infection, whereas all of the controls except one gained well. Seventy per cent of the rachitic rats died and showed evidences of pneumonia, and none of the controls with vitamin D died. All of the deaths occurred within six weeks after the animals were placed on the diet. The infecting organism was recovered from some of the dead animals, and from a microscopic examination of the pneumonic areas it appears that this organism causes a characteristic patho-

logical picture The failure to recover the organism from all the dead animals was probably due to faulty technic which has now been improved

The experiment is being repeated at present and the results to date are confirmatory

The effect of the substitution of 17 per cent casein (the main protein in milk) for 17 per cent wheat gluten (a good cereal protein) on resistance to infection was tested The diet was rickets-producing, and the calcium and phosphorus ratio was kept constant The rats which received the casein containing diet grew on the average considerably better (40 per cent) than those fed the diet containing wheat gluten Moreover, when their resistance to an oral infection with rat typhoid was compared after four weeks on the diets, there was a striking difference in favor of the casein, as in most of the experiments rats fed the wheat gluten died One would be tempted to say that the greatly increased resistance of the casein fed rats was out of all proportion to the moderate increase in weight which the casein produced Biochemists have convincingly shown that milk proteins greatly enhance the food value of cereals, and this work suggests that they also increase resistance to infection

The effect of an iron deficiency in lowering resistance against infection in humans has been strikingly demonstrated by Dr Helen Mackay

DENTAL CARIES

During the past 20 years numerous surveys have indicated that approximately 95 per cent of children suffer from this disease At the present time there is probably no other disease to which the human body is subject that is so wide-spread or so fraught with potential danger to the health of the individual

There is, of course, a marked diversity of opinion as to what is the cause of experimental caries, as a lack of various vitamins, an excess of vitamin D, a deficient supply of the minerals, calcium and phosphorus, and the consistency of the food have all been considered etiological factors in the development of this disease

In 1927 Drs Gordon and Mary Agnew of West China Union University in Chengtu, Szechwan, China, attempted the experimental production of caries in rats by feeding a diet low in vitamin D After also making several thousand observations on the hill tribesmen of Eastern Tibet and the villagers of West China, they joined us in the Department of Paediatrics, University of Toronto, in 1930 in a rather extensive program In approaching the problem of producing dental caries in animals by nutritional means, it was felt advisable to make as few variations in the diet as possible It has been previously pointed out that there are at least 37 different elements necessary for normal nutrition While a lack of any of these substances will interfere with the health of the animal as a whole, the close relationship between certain of these elements and definite pathological conditions is well recognized For instance, the relation of iodine to the production of goiter,

of vitamin C to scurvy, of vitamin D to rickets, and iron and copper to anemia. It is not unreasonable, therefore, to consider that a limited number of these elements may be intimately connected with the normal nutrition of the tooth, and conversely that a lack of these elements may result in the development of certain disease conditions, including caries.

From the results of these many hundreds of gross and microscopical examinations of the rats' teeth, it was found that if vitamin D be present in the proper amount, but phosphorus be slightly deficient, the vitamin will prevent decay. If the phosphorus be very low, vitamin D may delay but cannot prevent the carious process. Sugar, so long blamed for caries, has been proved harmless in the rat, to which diets have been given containing as high as 62 per cent carbohydrate but including also adequate minerals and vitamins. The danger of excessive sweets in the diet, as far as dental decay is concerned, seems to be in the tendency for sweets to dull the appetite for the phosphorus containing foods, such as egg yolk, milk, meats, leafy vegetables and grains.

It is realized fully that the value of this work lies in its application to man. Accordingly, a total of approximately 350 children on diets containing varying amounts of calcium, phosphorus and vitamin D, have been observed during the past year in four institutions, with the aid of a group of dentists of Toronto. A most meticulous dental examination was carried out at the beginning of the investigation and will be repeated at its conclusion. During the period of the investigation the children have been divided into three groups as follows: (a) the control group, in which no change has been made in the diet, (b) a group who have been given additional vitamin D, and (c) a group who have been given both additional vitamin D and phosphorus. An interim examination has recently been made of the children in groups (a) and (b). To insure an unbiased interpretation of results, operators in examining the children were unaware of the groups into which the children were classified until all the records were completed. This examination showed in those children who had been given additional vitamin D a definite trend toward a lessened incidence of caries as compared to those who had eaten only the usual normal diet. Moreover, the children with added vitamin D showed that previously existing cavities had been largely arrested. In certain of these arrested cases a definite hardening of the cavity walls was apparent. The general tone of the gingivae and of the mucous membranes of the mouth of these children showed a definite improvement when compared with the gingivae and mucous membranes of those children who had not been given the additional supply of vitamin D.

From the observations on rats it may be concluded that for the first time true dental caries, indistinguishable from the human, has been produced experimentally, and that it may either be cured or prevented by adequate amounts of both vitamin D and phosphorus in the diet.

As already mentioned, vitamin D is not present in perceptible amounts in ordinary table foods, with the exception of small and variable amounts

in egg yolk and summer milk. Our tests show that eggs procured in the open market in Toronto in the month of March contained as little as two Steenbock vitamin D units per egg yolk. (One dram of standard cod-liver oil contains 46 Steenbock vitamin D units.) As physicians, we all know that we see extremely severe rickets in the winter months in infants receiving as much as one quart of milk per day. This makes it plainly evident that the human race does not depend on ordinary foods for its source of vitamin D. As shown in recent years, we depend on the ultra-violet rays of sunshine and skyshine to produce this vitamin in our bodies.

We have studied the variations in the anti-rachitic value of sunshine in Toronto over a period of some years, and found that the anti-rachitic potency of summer sunshine was approximately eight times as great as winter sunshine. The chief deciding factor in this change in potency is the altitude of the sun above the horizon. It was found that when the sun was below 35° it produced only a slight effect as compared to the effect produced when above 35° . In Toronto, even in the middle of the day, the sun is always below 35° for four months of the year, in the latitude of London this occurs for five months of the year, and in the latitude of Glasgow for six months of the year. This means that in Great Britain for five to six months of the year the sun has only a slight anti-rachitic effect.

This, combined with modern methods of living indoors, and the smoke pall over the large cities, makes it plainly evident that unless some special means are taken, the average individual will not receive an amount of vitamin D commensurate with optimal health.

The use of cod-liver oil and other vitamin D products obtained through the drug stores, has increased greatly in recent years, with a resultant improvement in the health of the rising generation. We have been accustomed, possibly, to think only of the anti-rachitic effect of vitamin D, the recent work of May Mellanby in Great Britain and McCollum in the United States has shown conclusively the value of vitamin D in the prevention of dental caries. It is inconceivable that a vitamin so essential for life in the early years should not be essential throughout childhood and adult life, although in a decreasing amount.

Taking all these facts into consideration, we felt that if an additional supply of vitamin D could be made available to the public which would be obtained by them at no additional cost, and by no effort on their part, we would be doing something well worth while. Accordingly, we incorporated vitamin D, in the form of irradiated ergosterol dissolved in corn oil, in the shortening used in making bread, so that each 24 ounce loaf contained the vitamin D equivalent of 3 drams of cod-liver oil. This bread is now being produced in some 15 cities in Canada and some 68 cities in the United States. (Figures 2 and 3.)

It has been stated that cereal grains furnish from 30 to 60 per cent of the calories of the average diet. Most cereal products as used today are highly refined and contain only a small amount of minerals, and are almost



2



3

FIG 2 Roentgenogram of leg of rat fed on Steenbock's rickets-producing diet, containing 20 per cent of ordinary white bread. Blood phosphorus 2.0 mg per 100 c.c., percentage of ash in bones 30.1

FIG 3 Roentgenogram of leg of rat fed on Steenbock's rickets-producing diet, containing 20 per cent vitamin D bread. Blood phosphorus 4.6 mg per 100 c.c., percentage of ash in bones 49.5

devoid of vitamins. This, combined with the rather extensive use of refined sugars, which are quite devoid of both minerals and vitamins, makes it evident that a very severe strain is placed on the remaining portion of the diet to furnish an adequate supply of both vitamins and minerals. In view of these facts, we felt that if an infant cereal, or breakfast cereal, could be devised which, in addition to supplying calories, would furnish minerals and vitamins in appreciable amounts, it should prove to be a valuable addition in the average dietary. However, on account of the general preference for refined and finely milled cereals, it was felt that in order to be generally used, the cereal should resemble these widely used products in taste, appearance, non-laxative effect and keeping qualities. Accordingly, a cereal has been devised that fulfills these requirements, and has the following composition: wheat meal (farina), 53%; oat meal, 18%; corn meal, 10%; wheat germ, 15%; bone meal, 2%; dried brewers' yeast, 1%; alfalfa, 1%. The wheat

germ is used on account of its high protein, mineral and vitamin content. It contains a moderate amount of vitamin A and is exceptionally rich in vitamins B₁ and B₂, and is the most concentrated known source of vitamin E. Dried brewers' yeast supplies vitamins B₁ and B₂, in addition to the amount already furnished by the wheat germ. Alfalfa is added on account of its high vitamin A and mineral content. We have found that one per cent of machine dried alfalfa furnished sufficient vitamin A for the cure of xerophthalmia in rats. The iron content of alfalfa is more than 130 mg per hundred grams, which is 10 times the amount found in egg yolk, one of our most concentrated sources of iron in commonly used foods. The bone meal, which is an odorless, tasteless, white powder, is used on account of its high calcium and iron content. This cereal mixture has been used exclusively for the past two years in the Hospital for Sick Children, Toronto, and is also extensively used throughout the United States and Canada. In the infant wards, from the standpoint of a laxative, no difference was noted from the results obtained with the refined and finely milled cereals ordinarily used. The palatability of the product was evidenced by its being eaten with the same avidity as the ordinary cereal, not only by the infants, but also by the older children.

A study was made of the rate of growth of children fed daily two ounces by dry weight, of this cereal mixture in place of ordinary cereals. Some 20 children in all were taken and divided into two groups, one group fed the ordinary cereals in a well-balanced diet, and the other group fed the special cereal mixture in the same well-balanced diet. The children were kept under identical conditions and weighed at weekly intervals over a period of 10 weeks. At the end of 10 weeks the groups were changed, and the ones on ordinary cereals now received the special cereal mixture and the ones on the special cereal mixture received ordinary cereals. Their weights were observed over an additional ten-week period. The results obtained are shown graphically in figure 4. It is to be noted that on the special cereal mixture the children gained four to five times their expected rate, in contrast with the average rate of gain obtained while on ordinary cereals.

We believe that more care should be given to insure an adequate supply of both minerals and vitamins in the diet. The importance of these food essentials in the maintenance of normal growth and resistance against infection is not as widely recognized as it should be. We, unfortunately, do not know the exact requirements of these food essentials. We also do not know the exact amounts furnished by many foods. We do know, however, that, due to the ease with which we can obtain purified carbohydrates, we are apt to suffer from insufficient amounts of minerals and vitamins, and, in occasional cases, of proteins. Nevertheless, we can go a long way towards overcoming the deficiencies so frequently encountered in the average diet if we build up our meals around five essential articles of food, namely, milk, to supply calcium and protein, meat, to supply protein, eggs, to supply

protein, vitamins and iron, and vegetables and fruit, to supply minerals and vitamins. The remaining calories required can be furnished readily by the refined cereal and sugar products.

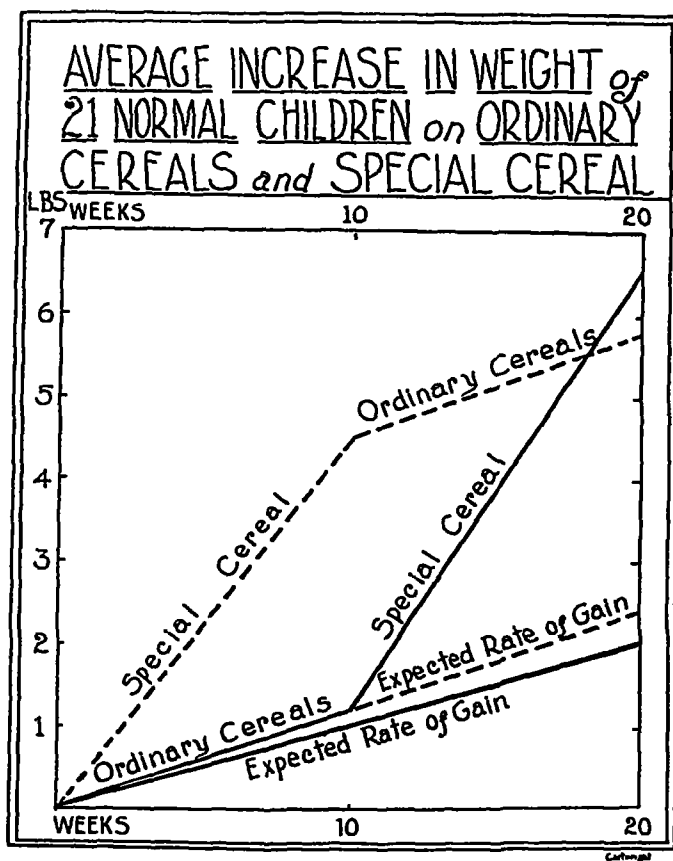


FIG 4 Comparison of the increase in weight of children fed the special cereal and ordinary cereals

After many years of practical experience, we are prepared to say that a more wide-spread observance of these few simple fundamental principles will go a long way towards improving the health of the community, and will materially assist us in reaching that goal which is the key-note of preventive medicine, namely, optimal health.

REFERENCES

- MACKAY, H M M Nutritional anemia in infancy, Special Report, Series 157, Medical Research Council
- ROBERTSON, E C, and ROSS, J R Increased resistance of rachitic rats fed irradiated food, *Proc Soc Exper Biol and Med*, 1930, xxvii, 999-1002
- ROSE, M S The foundations of nutrition, 1929, Macmillan Co, New York
- ROSS, J R, and ROBERTSON, E C Effect of vitamin B complex on resistance of rats to enteritidis infection, *Am Jr Dis Child*, 1932, xliii, 547-554
- SHERMAN, H C Chemistry of food and nutrition, Ed 3, 1928, Macmillan Co, New York

- SUMMERFELDT, P Value of increased supply of vitamin B₁ and iron in diet of children,
Am Jr Dis Child, 1932, xliii, 284-290
- TISDALL, F F, and BROWN, A Relation of altitude of sun to its antirachitic effect,
Jr Am Med Assoc, 1929, xcii, 860-864
- TISDALL, F F, DRAKE, T G H, and BROWN, A New cereal mixture containing vitamins and mineral elements, Am Jr Dis Child, 1930, xl, 791-799
- TISDALL, F F, DRAKE, T G H, and BROWN, A Incorporation of vitamins in bread,
Canad Med Assoc Jr, 1931, xxiv, 210-213
- TISDALL, F F, and BROWN, A Seasonal variation of antirachitic effect of sunshine,
Am Jr Dis Child, 1927, xxvii, 721-736
- TISDALL, F F, and BROWN, A Seasonal variation of antirachitic effect of sunshine,
Am Jr Dis Child, 1928, xxxvi, 734-739
- TISDALL, F F, and BROWN, A Seasonal variation in antirachitic effect of sunshine,
Am Jr Dis Child, 1931, xlii, 1144-1147

FURTHER OBSERVATIONS ON THE TREATMENT OF PERNICIOUS ANEMIA WITH PARENTERAL HORSE LIVER EXTRACT*

INCLUDING ONE CASE OF PERNICIOUS ANEMIA FOLLOWING GASTRECTOMY

By OSCAR RICHTER, M D , ARTHUR E MEYER, PH D , and
ANDREW C IVY, M D , PH D , F A C P ,
Chicago, Illinois

RECENTLY we¹ have reported that excellent remissions can be obtained in pernicious anemia patients with low blood counts from the subcutaneous or intravenous injections of a potent, highly purified horse liver extract. This communication entails a report of our observations on the further use of this injectable liver extract in 46 patients with pernicious anemia, covering a period of one year, during which time several thousand injections were given without local or systemic reaction. Although the oral administration of whole liver, liver extracts, and stomach substance are of unquestionable value in the treatment and maintenance of patients with pernicious anemia, the use of a potent injectable liver material in certain conditions is of decided advantage, and in many instances, a life-saving measure.

Cohn, Minot, and their associates,² as early as 1929, prepared a fraction from liver sufficiently pure to inject intravenously, which on administration produced maximal reticulocyte responses and a prompt increase in red blood cells. However, the large amount of material necessary to obtain this potent injectable liver fraction made it impractical from an economic standpoint for universal clinical use. Gansslen,³ in 1930, was able to obtain good responses in the treatment of pernicious anemia patients from the daily intramuscular injection of an extract from five grams of liver. Castle and Taylor⁴ reported maximal reticulocyte responses in two patients with pernicious anemia from a single intravenous injection of an extract prepared from 100 grams of liver. The unpleasant systemic reaction which occasionally followed the injection of this material, and the precautions necessary for its administration made it impractical and hazardous for general routine use. Later they⁵ described a method of preparing an extract of liver suitable for intramuscular injection, and reported on three cases, showing a maximal reticulocyte response between the fifth and seventh days from the daily intramuscular injection of the extract derived from 10 grams of liver. Favorable responses in the use of various parenteral liver extracts have been reported by Aubertin,⁶ Achard,⁷ van Leeuwen,⁸ Selander,⁹ Harrington,¹⁰ and others. Murphy¹¹ reported a series of 30 patients with pernicious anemia respond-

* Received for publication November 11, 1932.

This work was made possible by a grant from the Chappel Foundation for Organotherapeutic Research and was done at Northwestern University and Cook County Hospital Technician, Miss Helen Legere.

ing favorably to parenteral cattle liver extract. The material used in the majority of the cases was of a high concentration, so that 5 cubic centimeters contained the active principle derived from 100 grams of liver. Although the use of such a high concentration undoubtedly alleviates the necessity of frequent or daily injections, they were frequently followed by a great deal of local discomfort and occasionally systemic reaction, characterized by anorexia, faintness, palpitation, and fever. Strauss and Castle¹² in their latest report obtained favorable results in a large series of patients from the use of the parenteral liver extract which they previously described⁵ (2 cubic centimeters prepared from 10 grams of liver). In addition, they determined, from the treatment of 27 patients with varying single doses of parenteral cattle liver extract, that the amount necessary to produce a maximal reticulocyte response varies from the extract derived from 20 grams of liver to the amount derived from 100 grams.

PREPARATION OF THE PARENTERAL EQUINE LIVER EXTRACTS USED

The method of preparation which we previously described¹ was essentially similar to that of Strauss, Taylor, and Castle⁵. Absolute alcohol was added to the 70 per cent alcohol-soluble oral equine liver extract of known potency¹³. The resultant precipitate was dissolved in a convenient amount of water buffered with a phosphate mixture to make the solution isotonic and to adjust the pH of the finished product to 7.2. The solution was then filtered and 0.4 per cent tricresol was added as a preservative, and then standardized so that 1 cubic centimeter was equivalent to 10 grams of whole liver. Less than 400 milligrams of solid residue were present in the injectable extract prepared from 100 grams of liver.

We see no reason to believe that liver extracts made by different methods from equal amounts of liver will be equally potent. The present usage which seems to indicate the potency of a given preparation by a statement of the amount of liver used in its manufacture is misleading as pointed out previously by Meyer¹³.

METHOD OF ADMINISTRATION OF EQUINE LIVER EXTRACT AND SUMMARY OF PATIENTS TREATED

This report was made possible through the courtesy and cooperation of the medical staff of the Cook County Hospital who turned over to us patients with pernicious anemia. Each patient under observation received a careful clinical, laboratory, and roentgenological examination. All patients, with the exception of two, presented the classical picture of pernicious anemia with achlorhydria. Free acid was found in the repeated gastric analysis of the two patients, although the clinical and hematological findings were typical of pernicious anemia.

The majority of patients treated remained institutionalized until the hemoglobin and the red blood cell count became normal. Complete blood

and reticulocyte determinations were made at five day intervals after the institution of maintenance treatment. Reticulocytes were counted daily during the period of expected response. Of the 46 patients receiving the injectable equine liver extract, 27 entered the hospital during a blood relapse, so that in the majority of patients a definite reticulocyte response could be determined. Twelve patients with comparatively normal hemoglobin and red blood cell counts, who had been previously treated with whole liver or oral liver extract, were referred to the clinic for maintenance treatment. Two patients with blood relapses were treated with an injectable equine liver extract prepared four months prior to its use. This was done to determine any variation in potency that might occur after aging.

TREATMENT WITH INTRAVENOUS INJECTIONS

Complete blood remissions were induced in three patients with pernicious anemia by the intravenous administration of the equine liver extract (table 1, cases 3, 6, and 11). From 2 to 4 cubic centimeters (1 cubic centimeter pre-

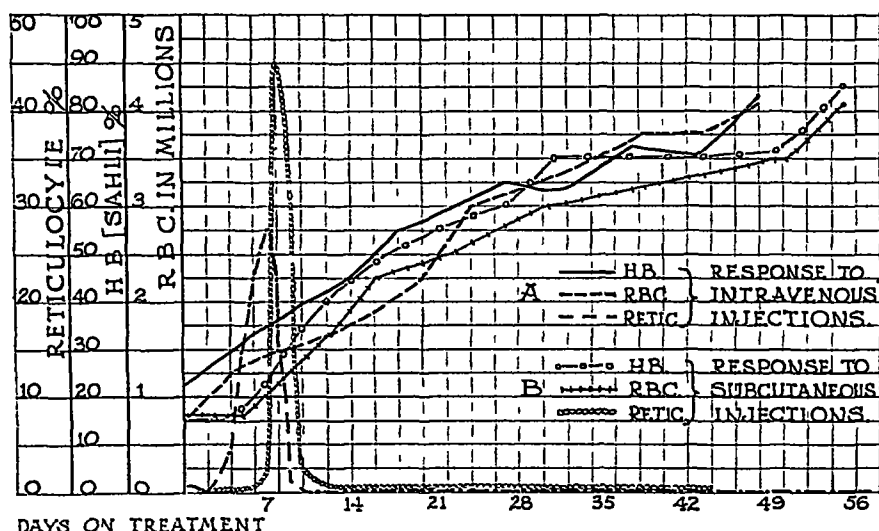


CHART I

pared from 10 grams of liver) of the material were injected at from one to three day intervals. Following the rapid injection of liver extract in the low-count patient, case 3, with an initial hemoglobin of 24 per cent and a red blood cell count of 840,000, a mild systemic reaction was occasionally noted. This consisted of an immediate drop in blood pressure, accompanied by a rapid, weak pulse, and dyspnea, and later followed by a generalized feeling of warmth. This systemic reaction was usually absent when the liver extract was injected slowly, i.e., less than 1 cubic centimeter per minute. No serious reactions were observed from a total of 60 intravenous injections. One of the three patients, previously resistant to treatment with large amounts of oral liver extract and whole liver (table 1, case 6), made a complete hematological remission in 57 days on intravenous injections of equine liver extract.

TABLE I
Primary Anemia
Responses of 22 Patients with Pernicious Anemia to Subcutaneous and Intravenous Injections of an Equine Liver Extract

No	Sex	Age	No of Re- lapses	Max Reti- culo- cyte %	Days on Treat- ment	Hemoglobin		Changes in R B C		Total Dos- age	Average Dose and Injection Route	** C N S Changes	Comments
						Be- fore	After	Be- fore	After				
††1	F	51	1	25.2	58	25	80	830	4.31	110 cc	2 cc Subc	Mild	On maint 92 days Req 2½ cc q 4.3 days On whole liver for maintenance
2	F	46	1	21.8	70	22	80	640	4.05	135 cc	2¼ cc Subc (1.15)	Mod	
†3	F	60	2	27.6	48	24	83	840	4.17	91 cc	3 cc Ven	Mild	Rec'd total of 57 cc Ven Cont'd daily subc 2 cc ***
4	F	61	2	20.6	47	47	85	1.68	4.04	105 cc	2¼ cc Subc	Adv	On maint 63 days Req 2½ cc q 4.3 days
5	F	72	1	29.4	72	26	81	890	4.14	128 cc	2 cc Subc	Adv	Sent to Psychopathic Hosp Had marked mental changes
†6	F	68	3	*5	57	41	81	1.08	4.14	73½ cc	2¼ cc Ven	Mod	Rec'd 3 to 4 cc Ven at 2 to 4 day intervals***
7	F	70	2	36.2	41	21	82	780	4.05	82 cc	2¼ cc Subc	Adv	Still on treatment
8	M	49	1	16.8	72	14	77	550	3.79	169 cc	2¼ cc Subc	None	Also had hemiplegia***
9	F	55	1	*13.6	50	39	83	1.42	4.11	102½ cc	1 cc to 2¼ cc Subc	None	
10	M	33	1	47.2	45	17	83	750	4.15	100 cc	2 to 4 cc Subc	None	On maint 63 days Req 2½ cc q 2.5 days
†11	M	29	2	*12.4	46	47	94	1.75	4.59	40 cc	2¼ to 4 cc Ven	None	On maint 85 days Req 2½ cc q 10.5 days
12	M	52	2	*3	48	36	80	1.27	4.03	108 cc	2¼ cc Subc	Adv	***

TABLE I—Continued

13	M	41	2	27 6	63	32	86	1 21	4 14	141 c c	2½ c c Subc	Mod	On maint 34 days Req 2½ c c q 2 days Still in hosp with CNS changes Daily inj cont'd
14	F	56	2	*	58	45	83	1 77	4 03	124 c c	2½ c c Subc	Adv	On maint 66 days Req 2½ c c q 3 7 days Left hosp before treat completed
15	M	69	1	22 4	32	33	81	1 41	4 05	70 c c	2½ c c Subc	Adv	On maint 90 days Req 2½ c c q 3 3 days Left hosp before treat completed
16	F	68	1	31 8	43	21	63	910	3 06	130 c c	2 to 4½ c c Subc	Adv	On maint 90 days Req 2½ c c q 3 3 days Left hosp before treat completed
17	F	32	1	27 2	51	32	63	1 53	4 12	115 c c	2½ c c Subc	None	On maint 90 days Req 2½ c c q 3 3 days Left hosp before treat completed
18	M	45	1	34 6	40	23	62	920	3 27	110 c c	2½ to 5 c c Subc	Adv	2½ c c subc inj daily on maint treat
19	M	32	1	22 6	53	21	82	1 10	4 08	142 c c	2½ c c Subc	None	*** Still on treat 2½ c c daily subc inj This treat preceded by oral frozen liver ext 1 oz t i d
20	M	65	1	22 6	35	34	65	1 13	3 02	79 c c	2½ c c Subc	Mod	On maint 46 days Req 2½ c c q 3 1 days
21	M	57	2	27 6	69	18	71	610	3 50	139 c c	2½ c c Subc	None	
22	M	73	1	*	45	58	84	2 44	4 13	112 c c	2½ c c Subc	Mod	
TOTAL		441	2	1042	47	676	1719	25 510	85 39	2222			
AVERAGE PATIENT		27 6	47			30 7	78 1	1 159	3 881	101			
AVERAGE GAIN				47 4		676	1719	25 510	85 39	2222			
AVERAGE DAILY GAIN (Per Patient)				10% Hb (Sahli)		30 7	78 1	1 159	3 881	101	Aver Daily Dose 2 14 c c		

* Cases in which our treatment was preceded for several days by other treatments which have absorbed maximal reticulocyte peak ** In this column, none, mild, moderate, and advanced denote the degree of central nervous system changes present, if any, prior to treatment *** Did not return for maintenance treatment † Responses obtained from intravenous injections ‡ Also had bleeding cervical polyp removed while on liver treatment

Cases 2, 16, and 19 received a more concentrated and purified equine liver extract during the period of reticulocyte response (1 c c prepared from 15 grams of liver)

CASE REPORT

A markedly anemic-appearing white woman entered the hospital on June 14, 1929, in a semi-stuporous condition. The blood examination on entrance revealed a hemoglobin of 50 per cent and a red blood cell count of 1,100,000 and the characteristic blood findings of pernicious anemia. A complete remission was induced by the liver diet, and the patient was sent home on July 18, 1929, with a normal hemoglobin and red blood cell count. Two years later, June 10, 1931, she reentered the hospital complaining of nausea, vomiting, weakness, and numbness and tingling of the hands and feet. The patient stated that after leaving the hospital, she followed the liver diet haphazardly up to eight weeks before, when she developed an upper respiratory infection manifested by fever, chills, chest pains, cough, and expectoration, which was followed by the symptoms for which she reentered the hospital. The blood examination now revealed a hemoglobin of 73 per cent and a red blood cell count of 3,200,000. She was started on a standard accepted cattle liver extract, receiving the amount equivalent to 720 grams of whole liver. Although her symptoms subsided, she made comparatively little hematological progress while on treatment for 26 days, and was discharged on July 7th with a hemoglobin of 78 per cent and a red blood cell count of 3,360,000. Three months later, November 4, 1931, the patient reentered the hospital for the third time, with a complete blood relapse. The hemoglobin was 29 per cent and the red blood cell count 890,000. Three and one-half cubic centimeters of equine liver extract were injected intravenously at from one to three day intervals for a total of 23 injections. A complete hematological remission was produced in 57 days, the patient leaving the hospital on December 12, 1931, with a hemoglobin of 81 per cent and a red blood cell count of 4,140,000.

TREATMENT WITH SUBCUTANEOUS INJECTIONS OF HORSE LIVER EXTRACT

Equally as good responses were obtained from subcutaneous injections of this liver extract as when it was injected intravenously. The ease of administration and its harmless and bland nature when injected subcutaneously were decided advantages, making it ideal for routine therapy. About 3000 injections of equine liver extract have been given subcutaneously, and in no instance did a systemic reaction occur. No apparent local reaction was noted in the majority of patients. Occasionally a local erythema and a feeling of warmth followed the injection, and in the exceptional patient some local pain persisted for several hours. Because of these negligible reactions, patients on maintenance doses continued their treatment by self-medication, returning to the clinic at from two to six week intervals for a hematological check-up.

Twenty-four patients with relapses were treated with daily injections of subcutaneous liver extract. The average dose used was 2.5 cubic centimeters, containing the active principle of 25 grams of horse liver. Patients entering the hospital in a semi-comatose or moribund condition received two or three injections (50 to 75 grams) daily until evidence of a reticulocyte response was obtained, and then once daily until the hemoglobin and red blood cell counts became normal. These results are tabulated in table 1. The maximal reticulocyte response was obtained between the fifth and seventh days and varied in this series of cases from 16.8 per cent to 47.2 per cent. The average of the entire group was 27.6 per cent, omitting the pa-

tients who received previous therapy, which had absorbed the maximal reticulocyte peak. With the occurrence of a remission the usual signs of clinical improvement were noted. This was evidenced by the subsidence of gastrointestinal symptoms, followed by an increase in appetite, strength, and weight, and a gradual recovery of the patients' general condition to a state of normality.

TABLE II

Differential Findings from Blood of Pernicious Anemia Patients in Chart I before and after Treatment with Equine Liver Extract
(Case numbers correspond to case numbers in Table I)

Case	E**	Arneth Index* (% in 100 cells counted)						Total No of Lobes	Differential Count (% in 100 cells counted)						M (N R C)
		1	2	3	4	5	6		N	E	B	L			
1	B	0	4	33	49	13	1	374	47	0	0	51	2		
	A	2	4	36	42	13	3	369	42	4	0	47	7		
2	B	0	1	20	50	22	8	420	52	0	0	44	4		
	A	1	7	39	44	8	1	354	62	2	1	30	5		
3	B	0	1	11	44	31	13	444	72	0	0	22	6	4	
	A	1	4	46	45	3	1	348	55	4	0	39	2		
4	B	0	2	28	44	21	5	399	50	0	0	48	2	3	
	A	0	9	43	36	11	1	352	57	2	0	35	6		
5	B	0	8	42	47	7	1	371	64	2	0	30	4		
	A	1	2	37	46	14	0	370	60	2	0	35	3		
6	B	0	4	19	51	29	2	426	38	0	0	60	2	1	
	A	0	6	49	39	6	0	345	58	4	0	33	5		
7	B	0	0	24	44	25	7	415	63	0	0	35	2	1	
	A	0	18	39	36	6	1	333	74	3	0	15	7		
8	B	0	6	35	37	18	4	379	53	4	0	40	2		
	A	0	6	52	35	6	1	344	49	6	1	38	6		
9	B	1	4	25	44	23	3	384	58	0	0	39	3		
	A	0	5	33	47	12	3	375	45	0	0	52	3		
10	B	0	4	19	43	25	8	410	73	1	0	26	0		
	A	0	7	41	34	18	0	363	66	2	1	30	1		
11	B	0	4	52	32	12	0	352	41	0	0	56	3		
	A	0	7	53	35	4	1	336	52	4	0	40	4		
12	B	0	2	29	40	20	9	395	39	2	1	54	5	1	
	A	0	11	44	34	11	0	345	59	2	0	30	9		
13	B	0	3	22	40	28	7	414	83	0	0	16	1		
	A	0	2	32	45	18	3	388	80	3	0	11	6		
14	B	0	2	31	44	18	5	393	41	2	0	54	3		
	A	0	4	52	32	12	0	352	77	0	0	20	3		
15	B	0	9	40	36	9	6	363	65	2	0	29	4		
	A	0	13	37	40	10	0	347	45	10	1	40	4		
16	B	0	1	21	40	30	8	423	56	2	0	40	2	1	
	A	1	6	25	45	20	3	386	56	4	1	33	6		
17	B	0	4	33	37	20	6	390	41	0	0	57	3	2	
	A	3	15	61	17	3	1	293	51	2	0	42	5		
18	B	0	3	35	37	17	8	392	58	0	0	39	3		
	A	0	7	46	38	7	2	351	80	0	0	19	1		
20	B	0	3	28	35	24	10	410	50	0	0	48	2	2	
	A	1	7	41	37	10	4	362	66	5	0	23	6		
21	B	1	8	38	37	14	3	367	85	0	0	15	0		
	A	2	12	45	29	10	2	339	65	0	0	32	3		

* Neutrophilic granular cells classified according to number of nuclear lobes. The hemoglobin and red and white cell determinations are recorded in Table I. ** In this column "B" denotes before treatment, "A" denotes after treatment with equine liver extract. In the Differential Count columns, N denotes Neutrophils, E—Eosinophils, B—Basophils, L—Lymphocytes, M—Monocytes, N R C—Nucleated red cells.

Differential examination of the white cells prior to treatment of each patient showed a marked shift of Arneth's index to the right. The average number of nuclear lobes in 100 cells counted from a series of 20 patients was 391.5 (Table 2). During the period of the maximal reticulocyte response, when evidence of blood regeneration was most marked, a definite tendency for the nuclear index to shift toward normal was noted. This temporary reaction was due primarily to the immature cells, released from the stimulated and hyperactive bone-marrow, occurring at the onset of a remission. Following the end of the reticulocyte response, a gradual shift of Arneth's index to the right was again noted, the average number of nuclear lobes in 100 cells counted at the end of treatment being 352.6. This finding was persistent in the majority of patients even after a normal hemoglobin and red blood cell count was obtained, and, from our experience, indicated that only a temporary remission is obtained from liver therapy, and that maintenance treatment is necessary to prevent another relapse.

A complete hematological remission was produced in four to eight week intervals, the majority of the patients treated showing an average daily gain of 1 per cent hemoglobin (Sahli) and 57,914 red blood cells from the average daily injection of 2-14 cubic centimeters of equine liver extracts.

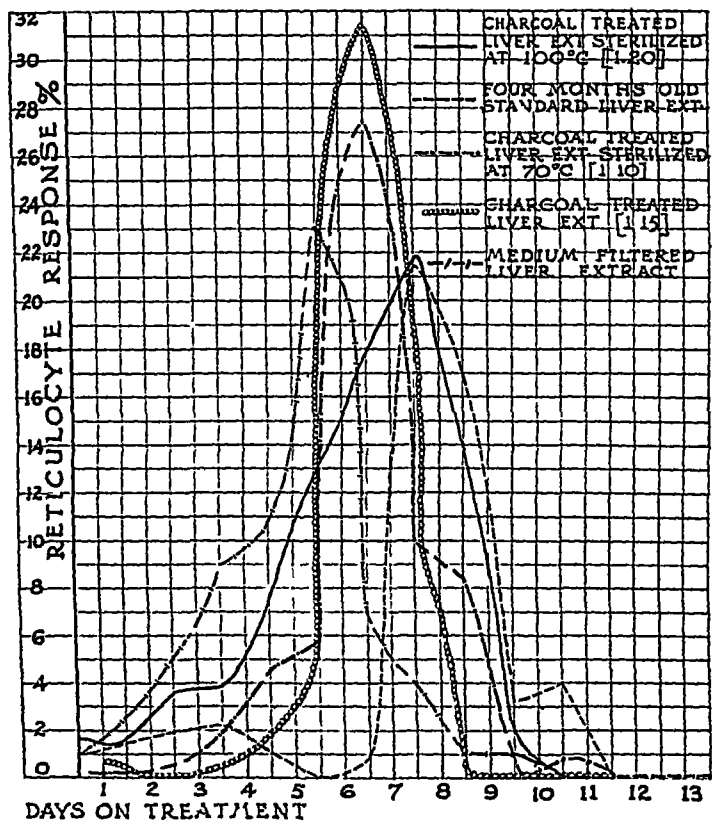


CHART II

RETICULOCYTE RESPONSES TO "OLD" AND SPECIALLY TREATED INJECTABLE EQUINE LIVER EXTRACTS *

In order to determine the potency of the standard equine liver extract after aging, two patients with pernicious anemia received daily injections of a four-month-old preparation. The responses observed in both cases were similar to those obtained from the freshly-prepared equine liver extract. The reticulocyte response of one patient is listed in chart 2.

Studies were also made on the effect of the standard extract, which had been treated by various methods in an attempt at further purification. Four such special preparations were used, the first was filtered through activated cocoanut charcoal and sterilized in ampoules at 100° C, the second was similarly treated with charcoal and subjected to fractional sterilization at 70° C, the third was filtered through hardened paper, S & S, and the fourth was ultra-filtered through a medium collodium membrane. In none of these special preparations was there any definite reduction in the percentage of solid residue. All produced prompt reticulocyte responses when injected subcutaneously into patients with pernicious anemia (Chart 2). It is apparent that aging, treatment with charcoal, sterilization by heat, and ultra-filtration through collodium membranes, do not affect the potency of the active anti-pernicious principle.

RESPONSES OF SEVEN CASES OF PERNICIOUS ANEMIA, WITH UNUSUAL COMPLICATIONS, TO SUBCUTANEOUS INJECTIONS OF EQUINE LIVER EXTRACT

This group included patients with pernicious anemia complicated by other diseases, which in several instances were of primary etiological importance and perhaps indirectly responsible for the anemia.

CASE I

A white female, 40 years of age, entered the hospital on December 16, 1931. From the history on record, the patient had previously entered the hospital four and one-half years before, during a blood relapse. At that time, in addition to the usual findings of pernicious anemia, a four plus spinal and blood Wassermann was obtained. The patient was given anti-luetic treatment, plus the liver diet. A complete remission was obtained, she was discharged from the hospital and advised to continue further anti-luetic treatment at a dispensary. For several years she conscientiously followed the anti-anemia diet. In addition, she received numerous courses of anti-luetic treatment, consisting of neoarsphenamine, bismuth, mercury, and iodides. The patient stated that for nine months prior to her present hospital entrance she had neglected to eat liver. After abandoning the liver diet, she began to feel weak and tired. This was followed by noticeable pallor, and loss of appetite and weight. The weakness became progressively worse, so that she was finally confined to bed. On admission to the hospital, the blood examination revealed a hemoglobin of 27 per cent and a red blood cell count of 780,000. Blood Wassermann and Kahn tests were negative. Treatment was started with daily subcutaneous injections of equine liver extract, and a complete remission was again produced in 77 days.

* Since this paper was submitted, batches of equine liver extract, aged one year, still showed evidence of retained potency.

TABLE III
Responses of Seven Cases of Pernicious Anemia with Unusual Complications to Subcutaneous Injections of Equine Liver Extract

Case	Sex	Age	No of Relapses	Max Retic- ulo- cyte %	Days on Treat- ment	Hemoglobin % (Sahl) Before	Changes in R B C			Total Dose	Average Dose and Injection Route	Complications
							After	Before	After			
1	F	40	2	7.8*	77	27	81	870	4.06	138 cc	2 cc Subc	Syphilis
2	M	59	1	*	26	65	80	296	4.17	54 cc	2 cc Subc	Septic arthritis
3	M	53	1	7.4*	75	40	75	119	3.09	201 cc	2 1/4 cc Subc	Ileo-cecal tuberculosis with ileo-colos- tomy
4	F	68	2	12.2	57	34	63	156	2.70	124 cc	2 1/4 cc Subc	Pyelonephritis and bronchopneumonia
5	M	63	1	27.4*	144	17	54	710	3.49	333 cc	2 1/4 cc Subc	Tuberculous bronchopneumonia
6	M	55	1	*	30	44	58	277	4.25	60 cc	2 cc Subc	Gastric syphilis subtotal gastrectomy
7	M	62	2	**	6	69	64	243	2.40	12 cc	2 cc Subc	Cancer of stomach with peritoneal and liver metastases

* In each case our treatment was preceded by other treatment, which had absorbed peak of reticulocyte response ** No reticulocyte response because of initial high hemoglobin and red blood cell count

CASE II

A white male, 59 years of age, entered the hospital on January 4, 1932, complaining of epigastric distress, frequent attacks of diarrhea, weakness, loss of appetite, and numbness and tingling of the hands and feet. On entrance, the blood examination revealed a hemoglobin of 35 per cent and a red blood cell count of 1,540,000. Treatment was started with equine oral liver extract, the patient receiving the extract equivalent to 720 grams of whole liver daily. A good hematological response was obtained. After the hemoglobin had risen to 65 per cent and the red blood cell count to 2,960,000, this treatment was replaced by daily injections of equine liver extract. Shortly after, while walking about, the patient injured his right knee. This was followed by swelling, redness, tenderness, and pain. Several days later the swelling became progressively worse and was associated with severe pain, tenderness, and a high temperature, with evidence of fluctuation over the knee joint. The knee joint was incised, and a large amount of pus was evacuated. The joint was drained for several weeks. A complete hematological recovery was obtained in 68 days on the combined treatment, and the patient was sent home on March 12, 1932, with a normal hemoglobin and red blood cell count.

CASE III

On April 6, 1932, a white male, 53 years of age, entered the hospital, complaining of weakness, abdominal cramps, diarrhea, and numbness and tingling of the hands and feet. The blood examination revealed a hemoglobin of 40 per cent and a red blood cell count of 1,190,000. The history obtained from the patient was that he had had frequent attacks of diarrhea for the past 15 years. Twelve years before he was seized by an attack of nausea, vomiting, and pain in the abdomen, which was diagnosed as an intestinal obstruction. An operation was performed, and on opening the abdomen a mass was found in the ileo-cecal region, which was diagnosed as tuberculous, and an ileo-colostomy was performed. Following the operation, the patient made a very slow recovery, remaining bedridden for three months, and at no time since did he regain his normal strength or weight. However, in spite of the persistent weakness and the continuous diarrhea, he was able to get around fairly comfortably for six years. He was then again seized with a similar attack of abdominal pain and fecal vomiting, which necessitated a second operation. Although he obtained relief from his obstructive symptoms, he was practically bedridden for a year, and required morphine and opiates for the relief of abdominal distress and diarrhea. At this time he was also severely anemic, for which he received injections of iron. Following this he was again able to be up and around, but the weakness and pallor persisted and became progressively worse, so that two years later he was admitted to a state institution. At that time his hemoglobin was 23 per cent and his red blood cell count 1,200,000. A diagnosis of pernicious anemia was made, and he was started on whole liver and liver extract by mouth. He was discharged from the hospital 12 weeks later with a hemoglobin of 70 per cent and a red blood cell count of 3,800,000, having also gained 22 pounds in weight. After leaving the hospital he felt fairly well, but he was unable to continue the liver diet and after six months re-entered the hospital with similar complaints. He was then transferred to another state institution, where he was confined for one and one-half years, during which time he definitely improved and felt fairly comfortable. He was again discharged and sent home on September 1, 1931. The patient failed to follow the liver diet at home, and had a gradual recurrence of symptoms, which became progressively worse, necessitating hospitalization. He entered our service on April 26, 1932. In addition to the characteristic blood findings of pernicious anemia previously described, a gastric analysis after an Ewald meal showed a free acidity of 38° and a total of 58°. The

blood Wassermann was negative. The gastrointestinal roentgen-rays showed no organic lesion in the cecum, although a definite fixation, suggestive of adhesions, of the cecum and ascending colon was noted. The patient received daily injections of subcutaneous equine liver extract. A reticulocyte response of only 7.4 was obtained on the eleventh day. However, a comparatively good hematological response later followed in spite of the persistent gastrointestinal disturbances, consisting of frequent attacks of abdominal pain and diarrhea. At the end of 73 days of equine liver extract therapy, the hemoglobin was 75 per cent and the red blood cell count 3,080,000.

CASE IV

A white female, 68 years of age, entered the hospital on February 24, 1932. From the history obtained, she had felt fairly well until a year before, when she began complaining of pain and numbness and tingling of the hands, and became unable to hold or grasp objects with security. Shortly afterwards, these symptoms were followed by weakness and dyspnea. Several weeks before admission she noticed swelling of the feet, and a sensation of bloating and epigastric distress. On entrance, the blood examination revealed a hemoglobin of 34 per cent and a red blood cell count of 1,560,000. The systolic blood pressure was 210 millimeters of mercury and the diastolic pressure 90. The blood Wassermann was negative. The icteric index was 16. Treatment was started with daily subcutaneous injections of equine liver extract. A reticulocyte response of 12.2 per cent occurred on the ninth day. Although a good hematological response was obtained after several weeks of treatment, the patient became semi-stuporous, gradually entered into uremic coma, and died 52 days after entrance to the hospital, with a hemoglobin of 63 per cent and a red blood cell count of 2,070,000.

CASE V

A markedly emaciated male, 63 years of age, entered the hospital in a semi-stuporous condition on December 21, 1931. The only history obtainable was that 16 years before the patient had been treated for pulmonary tuberculosis in a sanatorium and discharged as an arrested case. After this illness he had felt perfectly well until several months before admission, when he began complaining of weakness, epigastric distress, and attacks of nausea and vomiting. The blood examination on entrance revealed a hemoglobin of 22 per cent and a red blood cell count of 720,000. The blood findings were characteristic of primary anemia. The temperature was moderately high, ranging between 100° and 103.5° F. There was a persistent hacking cough, at times followed by the expectoration of mucopurulent sputum. After careful clinical and roentgenological examination, a diagnosis of tuberculous bronchopneumonia was made.

The patient received two injections of subcutaneous equine liver extract daily, equivalent to 50 grams of whole liver. In spite of the septic temperature, a reticulocyte response of 27.4 per cent was obtained on the sixth day. Although the bronchopneumonic process subsided, the patient still continued to follow the clinical course of an active pulmonary tuberculosis. During six months' stay in the hospital he received subcutaneous injections of equine liver extract twice daily. Because of the positive sputum, he was transferred to the tuberculosis hospital. The hemoglobin was then 53 per cent and the red blood cell count 3,340,000. Several days later he rapidly sank into a coma and died.

CASE VI

A severely anemic white male, 55 years of age, entered the hospital on October 7, 1931. The patient stated that on April 12, 1928, he had had a gastric resection per-

formed at the Research and Educational Hospitals. The summary of the clinical and laboratory findings present at that time were obtained from a report, published in 1929, by Dr H. Singer,¹⁴ his attending physician. The patient had then complained of abdominal pain and vomiting, which had been present for the preceding three years. For a few weeks before admission emesis had occurred five to six times daily, so that he had finally become unable to retain liquid foods. There had been marked loss of weight and extreme weakness. The gastric analysis after an Ewald meal showed an absence of free acid and a combined acidity of only five degrees. The hemoglobin was 68 per cent and the erythrocyte count was 4,100,000. The blood Wassermann and Kahn tests were four plus. The roentgen-ray examination with an opaque meal showed an obstructive lesion with an hour-glass constriction and canalization in the middle of the stomach, and marked gastric stasis. A possibility of gastric syphilis was strongly considered, and mercury and iodides were administered for several days. Because of lack of improvement in the symptoms of obstruction, a laparotomy was performed. A markedly thickened and shrunken stomach with an hour-glass constriction in its distal portion was found. An extensive resection was performed, leaving only the proximal 5 centimeters of the stomach. From the gross and microscopic examination of the resected portion, a diagnosis of gastric syphilis was made. Following the operation the patient made an uneventful recovery and was discharged from the hospital on April 21, 1928.

The history obtained regarding his present illness was that for two and one-half years after the operation he had remained comparatively well, his only complaint being a feeling of epigastric fullness after meals. He then, however, began to complain of weakness, palpitation, dyspnea, and numbness and tingling of the hands and feet. In the two months preceding his admission he had been unable to walk up two or three flights of stairs without becoming completely exhausted. Several days prior to his hospital entrance he had a mild attack of diarrhea. The blood examination on admission was characteristic of pernicious anemia, showing a hemoglobin of 22 per cent and a red blood cell count of 1,120,000. The blood Wassermann was four plus. The gastric analysis after an Ewald meal showed an absence of free and total acidity. There were definite objective sensory disturbances of both lower extremities. The patient was started on equine oral liver extract, receiving one ounce three times daily, which was equivalent to 720 grams of whole liver. An unusually slow increase in hemoglobin and red blood cells was obtained, so that at the end of 60 days on treatment his hemoglobin was 44 per cent and his erythrocyte count was 2,770,000. The oral liver extract was discontinued, and daily injections of subcutaneous equine liver extract were started. At the end of 30 days on this treatment a normal red blood cell count was obtained (4,250,000) with a hemoglobin of 58 per cent.

CASE VII

A white male, 62 years of age, entered the hospital on July 10, 1931. The patient stated that a year before he had begun to have pain in the epigastrium. The pain was described as dull in character. It radiated across the upper part of the abdomen, it usually occurred during or immediately after meals. This pain was occasionally associated with anorexia and vomiting. About two months before admission he began to suffer from weakness, dyspnea, and a numbness and tingling of the hands and feet. The blood examination on entrance revealed a hemoglobin of 16 per cent and a red blood cell count of 629,000, with other characteristic findings of pernicious anemia. He was placed on oral liver extract. He improved rapidly, and at the end of 72 days he was discharged from the hospital with a hemoglobin of 76 per cent and an erythrocyte count of 3,120,000. At this time no gastrointestinal examination was made. On July 12, 1932, he reentered the hospital, complaining

chiefly of severe epigastric pain, anorexia, and vomiting, occurring immediately after the intake of food. In the preceding six months he had lost 60 pounds in weight. He had noticed that occasionally he passed tarry stools. On entrance his hemoglobin was 69 per cent and the erythrocyte count was 2,430,000. Stomach analysis after an Ewald meal showed gross evidence of blood and an absence of free acid. Roentgen-ray examination revealed a mass involving the pars media of the stomach with retention. A diagnosis of carcinoma of the stomach was made. An exploratory operation was done on July 21, 1932, and a carcinoma was found involving the entire stomach from the cardiac to the pyloric end with metastasis to the liver and peritoneum.

It is apparent from the study of Cases 6 and 7 that the removal or destruction of the stomach wall was probably directly responsible for the subsequent anemia. Castle and his co-workers¹⁵ have definitely demonstrated that an activating substance essentially necessary for hematopoiesis and present in normal gastric secretion is absent in the gastric secretion of patients with pernicious anemia.

MAINTENANCE TREATMENT

The most difficult problem in the treatment of patients with pernicious anemia in a large institutional practice is maintenance. The majority of patients previously treated with the liver diet have at some time or other returned to the hospital in another relapse. This was usually due to neglect of their instructions to eat the necessary amount of liver, or to their inability to obtain the liver or an equivalent amount of liver extract. Occasional permanent remissions from liver therapy have been reported. The patients under our observation required continuous therapy to maintain their blood at a normal level. Twenty-six patients continued maintenance treatment with the injectable equine liver extract by self-medication, returning to the clinic at three week intervals for a hemoglobin and erythrocyte determination. During a period covering eight months of observation, the average dose required was two injections of equine liver extract a week. Our preliminary results indicate that the frequent injection of a potent anti-pernicious-anemia principle is more advantageous in maintaining a normal blood level and preventing complications than single large injections given every two or three weeks.

RESPONSE OF NEUROLOGICAL COMPLICATIONS

A subsidence of nervous symptoms was usually noted in patients with blood relapses following the institution of treatment with the injectable equine liver extract. In many instances a definite improvement of the mental and spinal cord symptoms was observed. Patients with subacute combined degeneration of the spinal cord showed definite subjective signs of improvement. Daily subcutaneous injections were continued in patients with cerebro-spinal symptoms even after the hemoglobin and red blood cell

count became normal. Because of the short duration of the period of observation of cases on this treatment, definite conclusions as to objective neurological improvement cannot be drawn at this time. A more detailed report will be made later, in association with Dr. Gonda, the attending neurologist, who has collaborated with us in this aspect of the treatment of patients with pernicious anemia.

ADVANTAGES OF SUBCUTANEOUS EQUINE LIVER EXTRACT THERAPY

The use of a potent and injectable material is of particular advantage in the treatment of the following types of cases: Patients with an aversion to liver, those who are vomiting, or are unable to assimilate orally administered preparations because of gastrointestinal dysfunction, stuporous or comatose patients, and uncooperative patients.

CONCLUSIONS

Forty-six patients with pernicious anemia treated with subcutaneous injections of equine liver extract were studied.

Twenty-two patients entering the hospital during a blood relapse, and treated with the parenteral equine liver extract made a prompt hematological and clinical recovery.

Favorable responses were obtained in five patients receiving special equine liver extract, showing that aging, sterilization at 100° C, and ultrafiltration did not affect the active anti-pernicious-anemia principle.

Seven patients with unusual complications, including one case of pernicious anemia following gastrectomy, treated with parenteral equine liver extracts, are discussed.

BIBLIOGRAPHY

- 1 MEYER, A. E., RICHTER, O., and IVY, A. C. The treatment of pernicious anemia with equine liver extract injectable either subcutaneously or intravenously, *Arch. Int. Med.*, 1932, 1, 538-543.
- 2 COHN, E. J., McMEEKIN, T. L., and MINOT, G. R. The nature of the material effective in pernicious anemia, *Am. Jr. Physiol.*, 1929, xc, 316-317.
- 3 GANSSLEN, M. Ein wirksamer, injizierbarer Leberextrakt, *Verhandl. d. deutsch. Gesellschaft f. inn. Med., Kong.*, 42, 1930, p. 524.
- 4 CASTLE, W. B., and TAYLOR, F. H. L. Intravenous use of extract of liver, maximal responses of reticulocytes from single injection derived from 100 grams of liver, preliminary communication, *Jr. Am. Med. Assoc.*, 1931, xcvi, 1198-1201.
- 5 STRAUSS, M. B., TAYLOR, F. H. L., and CASTLE, W. B. Intramuscular use of liver extract, maximal responses of reticulocytes from daily intramuscular injection of extract derived from 10 grams of liver, preliminary communication, *Jr. Am. Med. Assoc.*, 1931, xcvi, 313-314.
- 6 AUBERTIN, C., and VOILLEMINE. Anémie pernicieuse traitée par des injections intramusculaires d'extrait hépatique, *Bull. et mem. Soc. med. d'hôp. de Paris*, 1930, liv, 749-751.
- 7 ACHARD, C., and HAMBURGER, M. L'opothérapie hépatique par voie parentérale dans le traitement des anémies graves, *Presse med.*, 1930, xxxviii, 1273-1274.

- 8 VAN LEEUWEN, H C Treatment of pernicious anemia by intravenous administration of liver extract, *Nederl tijdschr v geneesk*, 1931, lxxv, 4425-4433
- 9 SELANDER, P Injectable liver preparation, *Hygeia*, 1931, xciii, 625-629
- 10 HARRINGTON, A W, and FLEMING, J Treatment of pernicious anemia by injections of liver extract, *Glasgow Med Jr*, 1931, cxvi, 345-351
- 11 MURPHY, W P The parenteral use of liver extract in pernicious anemia, *Jr Am Med Assoc*, 1932, xcvi, 1051-1060
- 12 STRAUSS, M B, and CASTLE, W B Parenteral liver therapy in the treatment of pernicious anemia, *Jr Am Med Assoc*, 1932, xcvi, 1620-1623
- 13 RICHTER, O, MEYER, A E, and IVY, A C Treatment of pernicious anemia with horse liver extract, preliminary report, *Jr Am Med Assoc*, 1932, xcvi, 1623-1625
- 14 SINGER, H A Syphilis of the stomach with special reference to its relationship to linitis plastica, *Am Jr Syph*, 1929, xiii, 391-410
- 15 CASTLE, W B, HEATH, C W, STRAUSS, M B, and TOWNSEND, W C The relationship of disorders of the digestive tract to anemia, *Jr Am Med Assoc*, 1931, xcvi, 904-907

RESEARCH IN ELECTROCARDIOGRAPHY*

By WILLIAM D REID, M D , F A C P , *Boston, Massachusetts*, and
SAMUEL H CALDWELL, Sc D , *Cambridge, Massachusetts*

A MODIFIED APPARATUS¹ and technic² for obtaining electrocardiograms was reported in 1932 This paper reports the further development of the apparatus and its use in electrocardiographic research

THE NEED FOR BETTER APPARATUS

The introduction of the string galvanometer by Einthoven in 1903 marked a great advance in the methods of recording rapid changes of small electric currents In most electrical engineering applications, however, the string galvanometer has been largely displaced by the oscillograph The latter instrument although by no means as sensitive as the string galvanometer is of a more sturdy design and can be adapted to give larger scale records with greater accuracy than can readily be obtained from a string galvanometer

Because the oscillograph is a less sensitive instrument, some form of amplifier must be used in conjunction with it because the electrical energy produced by heart action is not sufficient to operate an oscillograph vibrator element directly The factors which must be considered in designing such an amplifier have been discussed¹ previously

Three major considerations prompted the development of this apparatus The first of these was that although the quantity which concerns us in electrocardiographic studies is the potential difference produced during the heart beat, the quantity which a string galvanometer actually responds to is the current caused by that potential difference flowing in the vibrating string These two quantities although related are not necessarily directly proportional to each other Unless exact proportionality does exist, however, the string galvanometer deflection cannot possibly be proportional to the potential difference which causes it This lack of proportionality (or non-linearity, as it is usually called) may come about because the measuring circuit includes not only the substantially constant resistance of the galvanometer string but also the resistance of the body and contacts which may or may not be constant Furthermore these two resistances are of about the same size and the current through the string is therefore controlled just as much by the body and contact resistance as by the substantially constant resistance of the string

The fact that the body resistance varies from one person to another, and sometimes from one lead to another on the same person, leads to a procedure

* Read at the Montreal Meeting of the American College of Physicians, February 10, 1933

From the Evans Memorial of the Massachusetts Memorial Hospital, Boston, and the Massachusetts Institute of Technology, Cambridge, Massachusetts

in the use of the string galvanometer which in view of the second difficulty to be discussed is not at all satisfactory. In order to "standardize," it is frequently necessary to change the tension of the string. It is a well known fact that as the tension of a vibrating string is changed the natural frequency of vibration of the string changes also. The effect of changing the tension from one patient to another is therefore to alter the relative response of the string to current variations of different rates of change.

In describing current variations of the periodic type (such as are encountered in electrocardiography) it is customary to speak of the different harmonics or frequency components of the variation. It is well known that in speech and music we deal with sound waves which are of a very complex nature but which can be thought of as composed of a number of simpler oscillations which are harmonically related to each other, i.e., the frequencies are all simple integer multiples of the lowest or fundamental frequency. In a similar way the periodic wave which we get on an electrocardiographic record can be broken down mathematically (by a process known as harmonic analysis) into a number of simple sinusoidal oscillations which have frequencies related harmonically to the fundamental frequency. In the case of the electrocardiogram the fundamental frequency is the number of times per second the heart beats, say, about 1.25 cycles per second.

After we know by such a harmonic analysis the highest frequency component which is present to an appreciable degree in electrocardiograms, the range of frequencies to which a measuring instrument must respond is completely defined. Using the apparatus designed in this research, a typical normal* electrocardiogram was obtained and was then broken down by harmonic analysis, with the results shown in table 1.

TABLE I

Harmonic	Relative amplitude
Fundamental	1.00
2	2.36
20	3.24
30	0.75
35	1.27
40	2.27
45	1.33
50	0.94

It will be noted, for example, that the amplitude of the fortieth harmonic is more than twice as great as that of the fundamental. If the fundamental frequency is 1.25, then the frequency of the fortieth harmonic is $40 \times 1.25 = 50$ cycles per second. To carry this analysis still further an approximate pencil and paper analysis was carried out and it was found for example that the 100th harmonic (125 cycles per second) was about twice as large as the fundamental.

These findings indicate clearly that the shape of the electrocardiographic

* A conservative case was chosen. Many abnormal records contain high harmonics to a greater extent than was found here.

wave cannot be reproduced accurately by any instrument which fails to respond to these higher frequencies. In figure 1 is shown the results of a test made on a standard type of string galvanometer operating with normal tension on the string, as compared with the amplifier and oscillograph used in

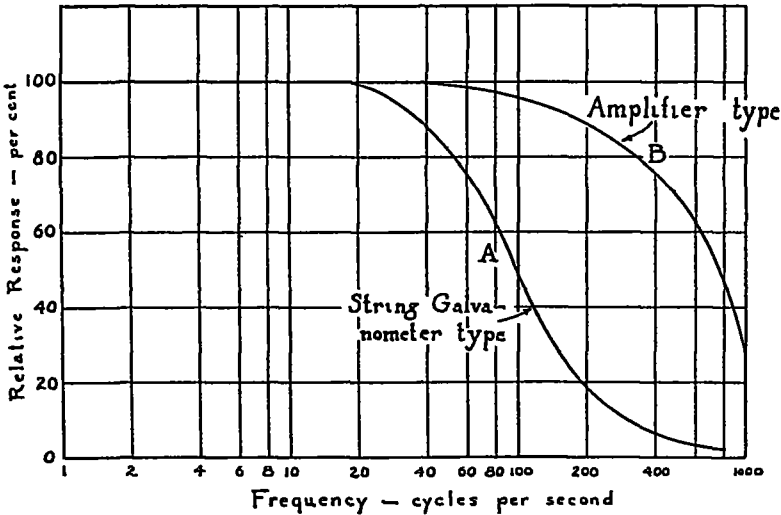


FIG 1 Comparison of the frequency response of a standard type of string galvanometer with that of the new amplifier type of electrocardiograph

this work. It will be observed that the response of both instruments falls off at the higher frequencies* but that the string galvanometer falls off much more rapidly than the other. If we are willing to tolerate as much as 15 per cent decrease in response, the string galvanometer used cannot be considered satisfactory for recording variations in which harmonics of 50 cycles or higher appear, while on the same basis the amplifier-oscillograph combination can be considered satisfactory up to 250 cycles, which is the 200th harmonic of the fundamental. This failure to respond to the important high frequencies is the second and by far the more important major difficulty encountered with the string galvanometer.

The objection has been raised that it is not necessary to use an amplifier and oscillograph in order to overcome this difficulty but that it is only necessary to increase the tension of the galvanometer string. While it is true that if the tension is increased the *relative* response of the string galvanometer will be improved at the higher frequencies, the absolute response or sensitivity will be decreased. If we are willing to tolerate a much smaller amplitude of record than is at present obtained, the frequency response of the string galvanometer can be materially improved, but of course the accuracy in the measurement of the smaller record will be less than at present.

The results of harmonic analysis shown above have been found to disagree with similar analyses made by other workers. One writer³ states that components beyond the fourth harmonic are of no importance, and our atten-

* The response of the amplifier oscillograph instrument has recently been considerably improved over that shown in the above figure.

tion has been called on various occasions to the lack of agreement between the results reported above and those formerly obtained. The explanation of this disagreement lies in the fact that the conflicting harmonic analyses were made on records produced by string galvanometers and not on records produced by instruments capable of passing high frequencies to an adequate extent. Obviously if the recording instrument in making its record does not respond to higher frequencies, mathematical analysis cannot make these frequencies appear in the record. The fact that there is a disagreement between the analyses made on these two types of records provides strong secondary evidence that the string galvanometer as *customarily used in electrocardiography* is not capable of responding to all the essential frequencies. To one well acquainted with harmonic analysis it is quite evident that the large rates of change of potential which appear in correctly reproduced electrocardiograms must be thought of as being produced by high frequency harmonic components, and if the recording instrument fails to respond to these high frequencies the final result cannot be a true picture of the phenomenon measured.

The third important consideration which led to the development of this apparatus was the small size of the electrocardiogram as usually obtained. If these curves are to be used for qualitative analysis only, there is no real need for a large size record. But if, as is actually the case, we are attempting to make a quantitative study of the records and base our conclusions on the numerical results, then it is obviously desirable to obtain a record which is large enough to permit accurate measurements without being so large as to be unwieldy and obscure. In the present work both the voltage scale and the time scale have been enlarged approximately by the same ratio. It is possible also to increase the time scale to the point where a single heart beat is recorded on a 36-inch record but this is considered a freak speed.

The record is traced with a narrow, sharply focused line rather than with the broad line so commonly seen on string galvanometer records.

THE APPARATUS USED

The original form of the apparatus has previously been described¹. It consists principally of a specially constructed vacuum tube amplifier and a standard type of oscillograph* using one supersensitive element for reproducing the electrocardiogram and a standard element for putting on the time wave.

* The bifilar oscillograph was chosen principally because it is readily available, relatively inexpensive, rugged, and easily maintained. Some workers have used oscillographs with a moving iron vane or needle. These must be carefully designed with respect to the magnetic properties of the iron, and the iron itself must be specially selected in order to obtain a linear response curve and also to avoid difficulty from hysteresis (if hysteresis is present to any appreciable extent, the deflections for *increasing* current will not be the same as those for *decreasing* current). The cathode-ray oscillograph offers great possibilities for experiment, but it is still very much in the developmental stage and is not as yet sufficiently reliable and trouble-proof to be used by the average technician.

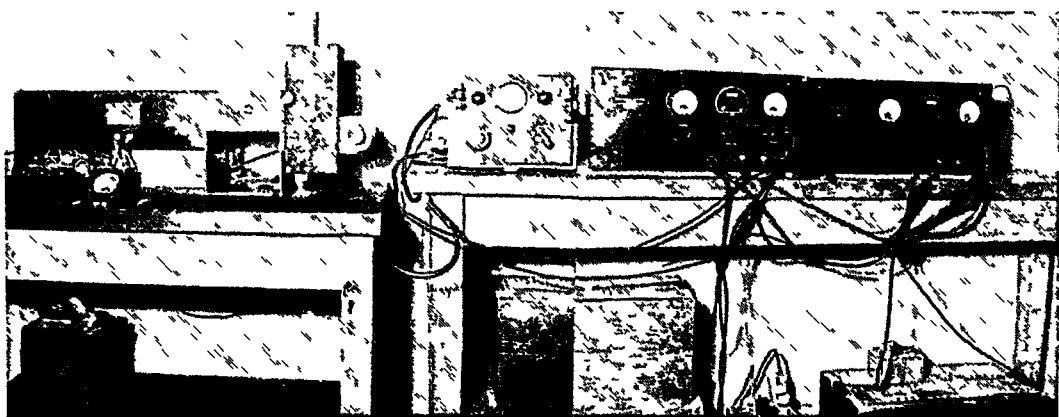


FIG 2 New apparatus Left to right oscillograph, control box, amplifier A, and amplifier B Batteries under the table

Recently a new apparatus (see figure 2) along the same lines has been built in which two amplifiers are used together with an oscillograph containing two supersensitive vibrators for recording the electrocardiograms and a single standard vibrator for the timing wave. A suitable switching and calibrating circuit is incorporated through which connections to the patient are made. In using this apparatus the records are made in pairs, the actual procedure is to record Leads I and II and then Leads I and III. By this arrangement it is possible to obtain the exact time relations between the voltages in the leads without recording all three leads simultaneously. The record is made on an inexpensive recording paper five inches in width, a camera was specially designed to carry a 25-yard roll of the paper and is arranged so that a single record can be cut off and developed without removing the camera from the oscillograph.

Space does not permit an adequate discussion of the amplifier as used but it should be emphasized that great care is required to build a successful high-gain amplifier for electrocardiographic applications. This is particularly true because the operation of the amplifier is to be recorded by an oscillograph and small variations which if present in a radio amplifier would be practically inaudible, are quite visible and disturbing if they appear on an oscillograph record.

By using an amplifier it is possible to eliminate almost completely the first difficulty discussed in the previous section, that is, the presence of body resistance in the measuring circuit. Instead of connecting the body in series with a resistance of comparable magnitude as in the string galvanometer method, the amplifier input circuit is designed so that it has a resistance about 100 times as large (250,000 ohms) as the average body resistance. Hence if the body resistance varied all the way from zero to its maximum value it could make no more than a small percentage change in the final result, and it is obvious that the ordinary variations which occur will have a negligible effect on the final record.

SUGGESTED NEW TECHNIC

It has become evident that the greater amplification and speed made available by this apparatus make visible details of the electrocardiogram which are inconspicuous or which cannot be seen in records taken by the standard technic. A few examples to show this are given (figures 3 and 6). Although it is possible to drive the camera with a speed at which a single

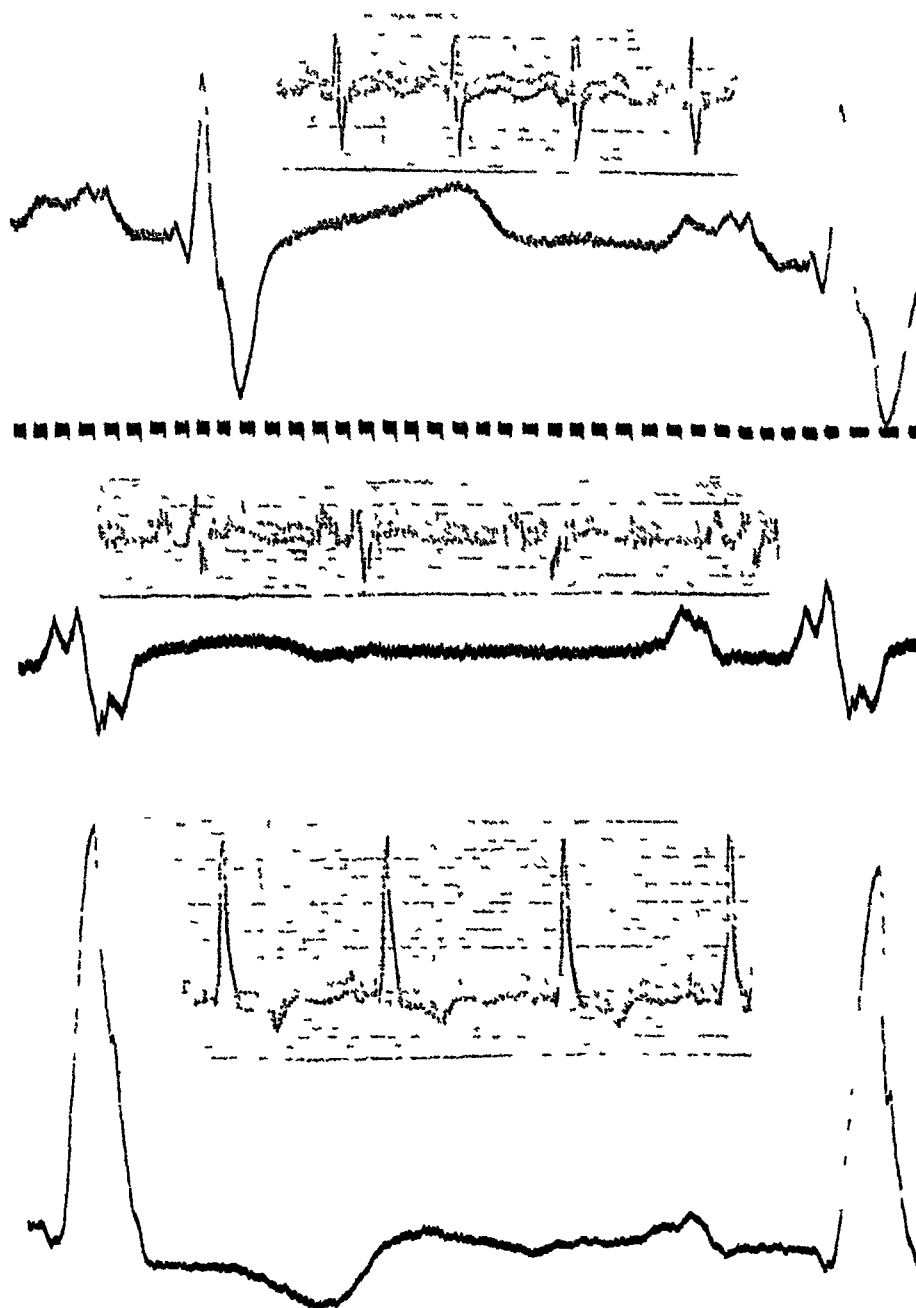


FIG 3 Short strips of three different electrocardiograms, with a section of the string galvanometer record from the same patient superimposed on each. The time record is shown only in the upper tracing. Note greater details and speed suggested as suitable in the new records.

heart beat is recorded on a 36-inch strip of paper, we have reached the opinion by study of numerous records that a more conservative speed is preferable. Figure 4 is included to show some of the variations in speed and the fact that the second notch in the P-wave is not visible until the record is spread out by using the higher speed.

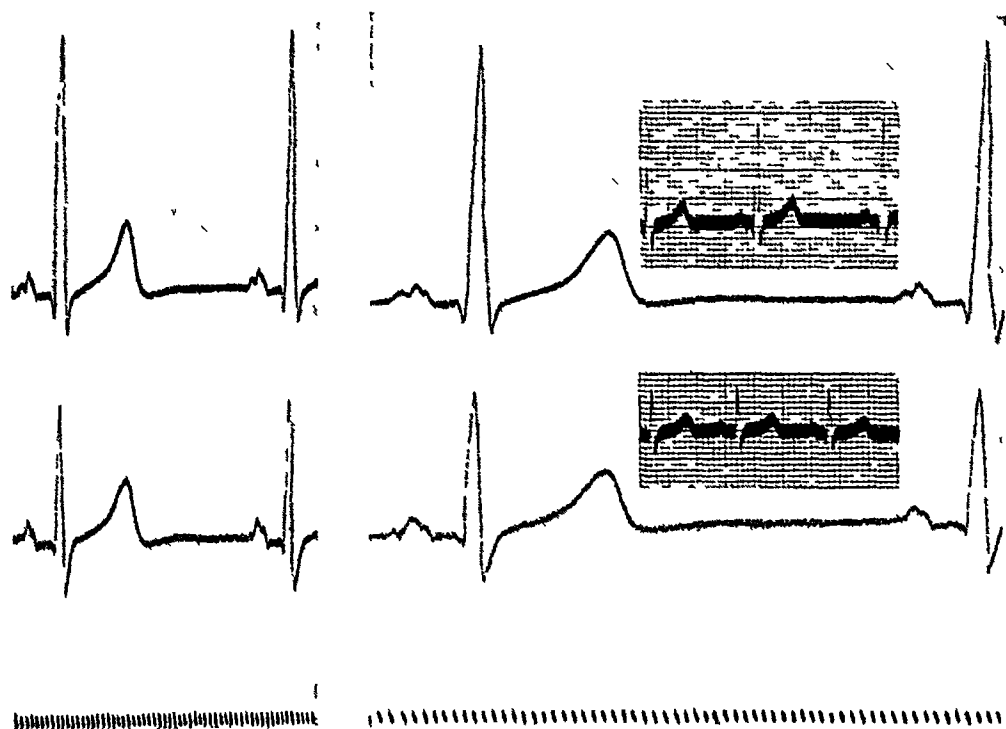


FIG 4 *Left* Lead II above, Lead I below, taken simultaneously. Time record at bottom. *Right* Same at greater speed, and with corresponding string galvanometer records superimposed. Note appearance of the second notching of the P-wave in the faster record of Lead II. Reduced by one-third.

The amplification is limited by the width of the photographic paper (five inches), that is, by the requirement that the largest wave recorded be inscribed on the paper. The ability to amplify the waves, without loss of accuracy in contour, appears to be of much assistance in disclosing their full details, especially in those instances in which the waves would otherwise be small. For example, see the accompanying illustrations.

It is suggested, therefore, that a technic be adopted that amplifies and spreads out the electrocardiogram so that all pertinent details may be studied and accurately measured.

NEW PROBLEMS

An analysis of the voltage recorded, or the amount of excursion from the baseline was made² on records taken from a series of 25 patients with the string galvanometer and with the new apparatus. The results are given in table 2.

TABLE II

Comparison of Voltage Recorded by the New Apparatus with That Recorded by an Einthoven String Galvanometer in a Series of 25 Patients

Wave	Status *	Number of leads †	Average difference ‡	Maximal difference ‡
P	same	19		
	lower	15	0 02	0 07
	higher	41	0 04	0 18
Q	same	37		
	lower	12	0 02	0 06
	higher	26	0 03	0 13
R	same	3		
	lower	24	0 09	0 34
	higher	48	0 19	0 90
S	same	34		
	lower	31	0 09	0 34
	higher	10	0 04	0 11
T	same	23		
	lower	12	0 03	0 05
	higher	40	0 03	0 15

* As compared with same wave recorded by string galvanometer

† Standard three leads for each patient, so number of leads equals 75

‡ In millivolts

Table 2 shows a difference in the voltage recorded in a large majority of the leads and in all waves, it was not constant in direction. The maximal difference found was 0.9 millivolt greater in an R-wave. This analysis shows clearly the large differences which can occur in recording and interpreting the same variation by the two methods. It is also noted that the differences in voltage we found were greater in frequency and in amount than those reported by Ernstene and Levine¹ in their comparison of a series of similar size between the string galvanometer and a commercial electrocardiograph using an amplifier and moving-ion oscillograph.

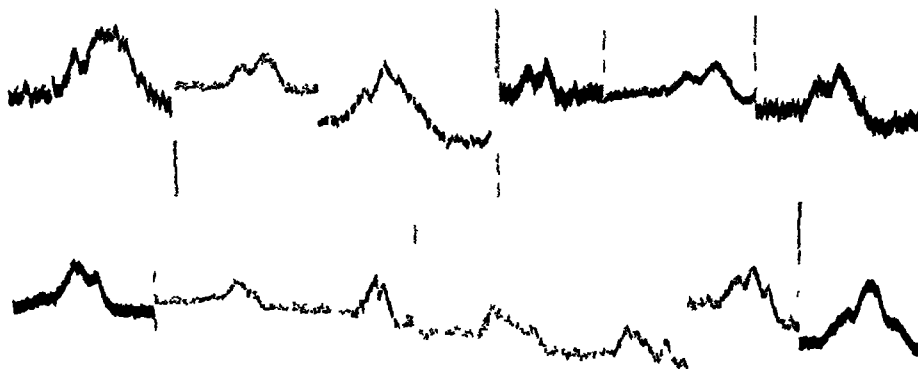


FIG 5 Series of P-waves. Upper row shows a single notch with the second peak the higher. Lower row shows the left-hand five P-waves also with a single notch but the initial peak the higher. The last two P-waves are indented twice and the middle peak is the highest of the three components.

The study of the details made visible by the new records is continuing. In figure 5 are shown a series of P-waves, they appear to be classifiable in groups according to the number of components made by the notches in them. In the upper row are six of these P-waves indented by a single notch and with the greater amplitude in the second component. In the lower row this condition is reversed in the first five examples, i.e., the waves are indented by a single notch but the first component, or peak, is higher. The last two of the lower row show three components with the middle one the highest.

Figure 6 contains examples of Q-R-S complexes showing the clarity

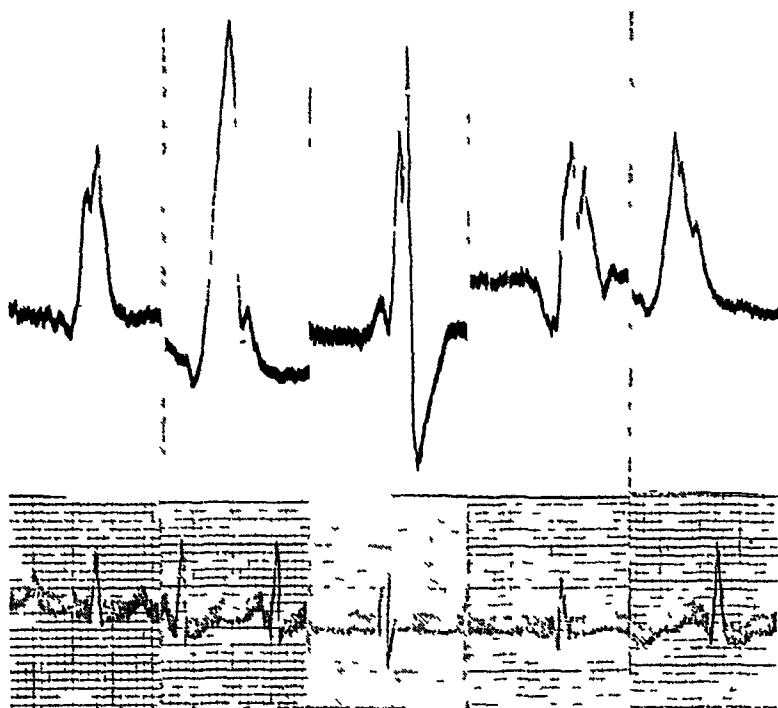


FIG 6 Series of Q-R-S complexes above with their corresponding string galvanometer records below each. Note absence of the small S-wave recorded in the two galvanometer records at left end of the series.

with which their various contours can be visualized. It is noted that the first two lack the small S-wave recorded in the string galvanometer record from the same two patients below. Examination of the standardization photographed on the string galvanometer record in these cases discloses a little overshooting which may reasonably account for the appearance of the S-wave on the record. In spite of considerable care in the technic of taking electrocardiograms with the string galvanometer, we have been unable to avoid this defect in some of the records taken with this instrument. Since becoming engaged with the work pertaining to the new instrument we have become increasingly conscious of this difficulty in constantly obtaining records free from overshooting when using the string galvanometer.

It is hoped that we may obtain a large number of records with the new

instrument taken on patients with coronary thrombosis in order to determine what new details, if any, may be disclosed in the progressive changes in the S-T interval and T-waves

It is of course impossible as yet to determine what significance may be placed upon these newly disclosed details of the electrocardiograms. The matter must wait for the correlation of a sufficient number of clinical and necropsy findings and, perhaps, some experimental work on animals. There is hope that new information of value may result, and it appears obvious that the only way to get the possible new light regarding the heart lies in continuance of the use of the new instrument.

From time to time various observers have reported the use of needle electrodes in the taking of electrocardiograms. We have persistently failed to obtain satisfactory records with the use of needle electrodes with the string galvanometer. The difficulty appears to be that when using needle electrodes we cannot obtain a satisfactory standardization, whenever we seek the deflection of 1 cm. for one millivolt imposed on the string the tension of the latter must be loosened so much that the string shadow tends to move off the field. This trouble which is presumably due to excessive polarization, has been so constant that we feel doubt as to the accuracy of the technic employed in records obtained with the use of needle electrodes and so believe these electrocardiograms to be distorted. As might be expected we found no difficulty in taking electrocardiograms with needle electrodes when using the new instrument. Such records are then the same as those taken with ordinary electrodes.

An application of the new apparatus has been made to physiologic research. Dr F. H. Pratt has recorded the beats of the lymph hearts of frogs. This has been done both with the lymph hearts in their normal position and with one of them after transplantation to the base of the tongue, where it resumed its rhythmic beating after the lapse of a few days although it no longer was propelling lymph. The beat of the transplanted lymph heart was found to more closely simulate that obtained directly from the ventricle of the frog's blood heart, than it did that of the lymph heart in its normal position and with its normal connections with the spinal cord. This work becomes more impressive when it is pointed out that the size of the lymph hearts in the frog varies from but one to two millimeters in diameter.

It may be of interest to add that these lymph hearts are possessed by all amphibia and reptiles. They assist in the forward propulsion of the lymph. In the case of the frog they occur in two pairs, the anterior located under the scapulae and the posterior just lateral to the vertebral column at the caudal end of the body. They beat at an average of sixty times per minute and in unison, their rhythm is controlled from the spinal cord with which they are connected by minute nerves. Some disturbances of rhythm, especially extrasystoles, have been produced in lymph hearts by experimental procedures.

SHOULD THE STRING GALVANOMETER BE DISCARDED FOR CLINICAL ELECTROCARDIOGRAPHY?

None of the above discussion is presented with the idea that the apparatus and technic developed should immediately supplant those used at present. On the contrary, there are good reasons for continuing with present equipment for some time. In the first place, clinical service must be maintained without interruption. The interpretation of electrocardiograms is largely an empirical process, based on the accumulated evidence of many cases. Before a new technic can be of real value, we must establish for it a basis of comparison from which sound conclusions can be drawn. So far as general characteristics are concerned, the experience gained with the string galvanometer is fully available for the interpretation of these newer records, but new details have appeared and before they can be properly interpreted much clinical and postmortem data must be gathered.

Furthermore, it is highly desirable to maintain a standard method so that the published work of different men may readily be compared. Until a majority of workers have recognized the real advance that the introduction of the vacuum tube has made possible in the measurement and recording of small variations in electric current and voltage, and have adopted these later technics, string galvanometer records must be used as a medium for exchange of ideas and discussion.

SUMMARY

The desirability of having better apparatus for electrocardiography is discussed. There are three major considerations:

- 1 The current which flows through the vibrating string of the Einthoven string galvanometer is not necessarily proportional to the potential differences set up during the heart beat.

- 2 The string galvanometer fails to respond adequately to important high frequencies. This is the most important major difficulty encountered with the string galvanometer.

- 3 The size of the record is suitable for qualitative analysis but not for accurate quantitative analysis of the phenomena studied.

A report is made of the further development of a new apparatus for electrocardiography. It consists principally of specially constructed vacuum tube amplifiers and a standard type of oscillograph. Records may be obtained with any two leads taken simultaneously.

A technic that amplifies and spreads out the electrocardiogram so that its full details may be seen is suggested.

A study is being made to determine the significance of the newly disclosed details of the electrocardiograms obtained by the new apparatus.

Satisfactory records have been obtained by the use of needle electrodes.

The new apparatus successfully records the potential differences set up by the beating of the minute lymph hearts of the frog.

The opinion is expressed that at present the Einthoven string galvanometer should not be discarded for clinical work. The technic of using the amplifier instrument must be firmly established and much comparative data must be collected before it can completely supplant the string galvanometer in electrocardiography.

BIBLIOGRAPHY

- 1 CALDWELL, S H, OLER, C B, and PETERS, J C, JR. An improved form of electrocardiograph, *Rev Scient Instruments*, 1932, iii, 277-286
- 2 REID, W D. Preliminary report on the use of an improved form of electrocardiograph, *Jr Lab and Clin Med*, 1932, xvii, 804-812
- 3 WIGGERS, C J. Principles and practice of electrocardiography, 1929, C V Mosby Company, St Louis, p 32
- 4 ERNSTENE, A C, AND LEVINE, S A. A comparison of records taken with the Einthoven string galvanometer and the amplifier-type electrocardiograph, *Am Heart Jr*, 1929, iv, 725-731

THE DIFFERENTIAL DIAGNOSIS OF DISEASES OF THE LIVER AND SPLEEN WITH THE AID OF ROENTGENOGRAPHY AFTER THE INTRA-VEINOUS INJECTION OF THORIUM DIOXIDE SOL (THOROTRAST): EXPERIENCE WITH EIGHTY PATIENTS*

By WALLACE M. YATER, M.D., F.A.C.P., and LAURENCE S. OTELL, M.D.,
Washington, D. C.

MANY REPORTS have appeared in medical literature within the last three years concerning results with a newly developed method of visualizing the liver and spleen. Einhorn and Stewart¹ were apparently the first to undertake the development of a method of this kind (1927). They made roentgen-ray films of the liver after the oral administration of tetraiodophenolphthalein and diiodoatophan and were able to demonstrate carcinoma and cirrhosis of the liver. The results, however, were not striking.

In 1928 Radt^{2, 3, 4, 5} in his clinic at the University of Berlin, began work to develop such a method on the basis of the theory that a colloidal material of high atomic weight when injected into the blood stream might be taken up by the reticulo-endothelial cells and allow roentgenographic visualization of the liver and spleen, the two organs of the body containing the greatest number of these cells. A thorium dioxide preparation called tordiol was first tried by Radt and by the Japanese investigator, Oka^{6, 7} but was discarded after use in animals because the solution was not stable and produced capillary emboli. Both men then turned to a somewhat similar preparation called thorium dioxide sol, which was found to be relatively harmless both in animals and in man. These investigators found that after the injection of this substance the size and contour of the liver and spleen were plainly visible, and in several cases they were able to determine the presence of metastatic carcinoma and of cirrhosis of the liver.

ANIMAL EXPERIMENTATION

A number of investigators have reported results of animal experimentation with thorium dioxide sol. The metal is removed from the blood stream several hours after intravenous injection by the cells of the reticulo-endothelial system in the liver, spleen, bone marrow, lymph nodes and to some extent in the lungs, heart, ovaries and adrenal glands. It is eliminated very slowly, in fact some of it may remain in the tissues for years. Various authors report different rates of elimination. The liver apparently loses the substance faster than other organs. Elimination may occur mainly through

* Read at the Montreal Meeting of the American College of Physicians, February 8, 1933.

From the Georgetown University and the Gallinger Municipal Hospitals and the Radiologic Clinic of Drs. Groover, Christie and Merritt.

the bile and urine as indicated by the work of Leipert,⁸ but apparently it may take place also by cellular transport to the lungs and be removed by the bronchial mucus as shown by Kadrnka⁹ and by Irwin¹⁰

Histologically the metal appears as greenish, refractive granules in the reticulo-endothelial cells, which appear globular and in which the nucleus is displaced to the periphery. The larger the dose the greater the engorgement of the cells.

Pathologic changes in animals thought to be due to the foreign substance have been reported by some investigators, but many have concluded that the damage is transitory or negligible. The work of Tripoli and Haam,¹¹ which has been personally followed to some extent by one of us (Yater), leads us to believe that in the dosage used in man there is no danger of direct injury due to the presence of the thorium dioxide in the tissues.

Lambin¹² studied the effect of injections in rabbits upon the blood picture. Moderate doses produced an erythroblastic reaction, while large doses produced a pronounced anemia, recovery from which was spontaneous. A phase of leukopenia followed the injections, but this changed to a longer phase of leukocytosis, first of granulocytes and later of monocytes. Popper and Klein¹³ in similar experiments did not find changes in the blood picture of any importance. Thrombocytopenic purpura was produced in several rabbits by Shih and Jung¹⁴ with doses of Thorotrast several times greater than those used in man. In this connection we have followed the platelet count in several of our patients following the injections, and have observed no significant changes.

The question concerning the effect of partial blockade of the reticulo-endothelial system by thorium dioxide sol on the immune reactions of the body to infection has been satisfactorily answered by Held,^{15, 16, 17} by Varalopez and Thorbeck,¹⁸ and by Randerath and Schlesinger.¹⁹ These workers concluded in the main that the presence of large amounts of the metal in the reticulo-endothelial cells has no very appreciable effect upon antibody formation, hemolysin titer, albumin-globulin coefficient, reciprocal storage capacity of the cells or in general upon the defense mechanism of the body against infection. One of us (Otell²⁰) has reviewed the subject of the physiology of the reticulo-endothelial system and has pointed out the various probable functions of these cells. Apparently none of these functions is seriously or even moderately impaired by the method under discussion.

RADIOACTIVITY OF THOROTRAST *

The Council on Pharmacy and Chemistry of the American Medical Association²¹ has recently not approved of the use of Thorotrast in man on the grounds of "very imperfect elimination, fairly high alpha-ray activity, the possibility of further increase in radioactivity by partial conversion to meso-

* Thorotrast is the trade name given by the Heyden Chemical Corporation to their stabilized, colloidal solution of thorium dioxide, which contains 25 per cent by volume of thorium dioxide. Thorotrast has been the preparation of thorium dioxide used by us and others for hepatosplenography.

thorium and radiothorium, and the possibility of sensitization of tissues to roentgen-rays" Seventy-five cubic centimeters of Thorotrast contain a quantity of thorium dioxide equivalent in alpha-ray activity to 15 to 30 micrograms of radium The beta-ray and gamma-ray activity of this amount of thorium dioxide is probably too feeble to be of physiologic significance, but the alpha-ray activity is thought to be sufficient to be a potential source of danger when dispersed through the tissues Proof of ill effects from this source, however, are thus far totally lacking, nor is there any published work which shows either that there is further increase in radioactivity with the passage of time or sensitization of tissues to roentgen-rays by Thorotrast Radt²² has observed no ill effects of any kind after three and a half years of extensive experience with Thorotrast both in animals and in man Neither have we observed any changes attributable to the presence of Thorotrast in the tissues of patients after one and a half years One patient with myeloid leukemia who has had seven roentgen-ray treatments during one and a half years following the injections of Thorotrast has remained in excellent condition and has not shown any evidence of sensitization to the roentgen-rays

REACTIONS DUE TO THOROTRAST

Reactions following the injection of Thorotrast into the blood stream have been few and mild Occasionally there is a slight transitory discomfort, mild tension of the limbs, chilly sensations, or a moderate rise in temperature Reactions attributable to the injection of Thorotrast occurred in only four of 80 patients on whom we used the method A patient with Banti's disease complained of severe pain in the lumbar region and chest followed by spasmodic contractions of the recti abdominis muscles which subsided without residual symptoms or signs Another patient complained of transient lumbar pain after the first injection A child had some puffiness of the eyelids and face for three days A fourth patient, who died as the result of hemorrhage from a traumatically ruptured spleen, had vomiting and transient collapse which may or may not have been due to the injection of Thorotrast

Bungeler and Krautwig²³ reported a case of fatal rupture of an enlarged spleen occurring 22 hours after a second injection of Thorotrast Many of our patients had enlarged spleens, but the only one who had a reaction was the one with Banti's disease

METHOD OF ADMINISTRATION

In adults of average size 25 cubic centimeters of Thorotrast are administered intravenously on each of three successive days In children the dose is reduced roughly in proportion to the weight More accurate estimation of dosage on the basis of body weight is apparently unnecessary In general the density of the roentgen shadows of the liver and spleen depends upon

the quantity of the medium administered and the anatomical and functional integrity of the cells that store it. If only the outlines of the liver and spleen are desired the dose may be reduced one half. Fractional doses are used in order to eliminate the shock which might be produced by the injection of too large a dose of foreign material.

Films may be taken at any time after four hours following the last injection. On the night before the examination the patient is given the usual evening meal and at bedtime eight grams of compound licorice powder. On the morning of the examination a cleansing enema is given and the patient is instructed to come to the roentgen-ray department without breakfast. Films are taken in both the prone and supine positions on the Potter-Buckley diaphragm. The tube is centered over the ensiform cartilage. The following technic has been used in patients of the average physique: 60 K V P at 100 m a for $3\frac{1}{2}$ seconds at 25 inch distance. It is well in most individuals to place the film transversely in order to get a good image of the spleen and liver on the same film. A more comprehensive idea of the structural characteristics of the liver and spleen is obtained by making several exposures within a range of 10 K V of this dosage. Careful technic is essential in securing films which show details of structural change.

NORMAL APPEARANCE AND SIZE OF THE LIVER AND SPLEEN

In good films the liver should cast a homogeneous shadow of approximately the same density as the spine. The spleen normally has a density slightly less than that of the liver shadow, and about the same as that of the ribs. In some cases the kidneys are well visualized.

In determining whether the liver and spleen are abnormal in size it is necessary to know what the average normal size of these organs is. We obtained very little help from the literature in this regard, and unfortunately a sufficient number of individuals without alteration of the liver and spleen has not been studied to form a basis for this comparison. The only work of any value in reference to the size of the liver is that of Pfahler,²⁴ who compiled tables of the size of the liver in subjects of both sexes, of different ages and of varying heights and weights. These data were computed from flat films of the abdomen. Pfahler found that there was very little variation in adults in the size of the liver as determined roentgenographically. Two measurements of the liver shadow were taken, one was the "length" which was measured from the highest point of the upper border to the lowest border of the tip of the right lobe, the second measurement was made obliquely from the upper border to the lower border in a direction which gave the maximum measurement of the apparent thickness of the liver. The average normal length of the liver shadow was 21.3 cm, with limits of approximately 18 to 22 cm, and the average oblique measurement was 12.8 cm, with limits of approximately 10 to 14 cm. These data, while the best available, are obviously inaccurate because of the indistinctness of the liver

shadow in such films. The measurements were only comparative, inasmuch as the short distance between the tube and the film (25 inches) produced some distortion.

After the use of Thorotrast the right lobe of the liver appears to constitute most of the organ. The left lobe looks very small and is frequently obscured by the shadow of the spine. The left extremity of the liver rarely extends more than 6 cm. to the left of the midline. It comes to an acute angle under the left leaf of the diaphragm. The presence of ascites may give a false impression of the size of the liver, causing it to appear smaller than it should.

Comparative determinations of the size of the spleen are still more difficult since the spleen normally varies a great deal in size from time to time. Also, in normal subjects after the injection of Thorotrast the spleen may not be well visualized because of gas in the stomach. Even in cases of splenomegaly there may be some difficulty with this method in accurately determining the limits of the spleen for the same reason. Nevertheless, after experience with the method one may be able fairly accurately to estimate the size of the spleen, and changes in the size of the spleen in the same individual may be followed. The spleen may be considered to be of normal size if it occupies the space of two ribs and two interspaces. For recording our measurements we have used the greatest dimension and the dimension taken at a right angle to this through the middle of the organ.

STUDY OF CASES

In November 1931 we²⁵ reported briefly on the study of this diagnostic method in eight cases. In this country Einhorn, Stewart and Illick²⁶ had just previously (July, 1931) reported their findings in nine cases. They²⁷ made a further report in January 1932 and stated that they had observed some severe but non-fatal reactions from the use of the method, one being hematemesis in a patient with Banti's disease and jaundice, which may have been due to the Thorotrast. In February 1932, Tripoli, Haam and Lehman²⁸ reported their use of the method in a patient and stated that they had not observed any reactions in 15 patients. We²⁹ presented our experience with the method in 40 cases at the annual convention of the American Medical Association in May 1932, stating that three non-fatal reactions had occurred. We are now reporting our experience with 40 more patients, a total of 80, with reactions in only four, as previously stated. All three groups of investigators commented upon the value of the method as an aid to diagnosis of diseases of the liver and spleen.

The 80 cases in our series included a number of conditions, but mostly they were instances of liver disease. Cirrhosis of the liver and metastatic carcinoma predominated. Of the 80 patients, 31 are known to have died in the natural course of their disease. Of these patients 19 came to necropsy, in 11 others, operation was performed and biopsy of the liver made

or splenectomy performed, while in seven more, operation was performed without biopsy. In 36 patients, therefore, an opportunity was afforded to verify the diagnosis. In many of the other cases the diagnosis was reasonably certain. It is felt that the value of this method of diagnosis can be fairly well vouchsafed from this study.

CASES IN WHICH THE VISUALIZATION METHOD WAS DIAGNOSTIC

Cirrhosis of the Liver There were nine cases of cirrhosis of the liver of Laennec's type in which the diagnosis could be positively made from roentgen-ray films alone. In three cases necropsy was performed. The size of the liver could be determined even when ascites made this estimation impossible by methods of physical diagnosis. In four cases the liver was shown to be smaller than normal, in two cases it was found to be enlarged, and in three cases it was apparently normal in size. Cirrhosis was indicated either by a diffuse mottling due usually to small, closely placed opaque areas (figure 1), or by much reduced density of a homogeneous liver shadow

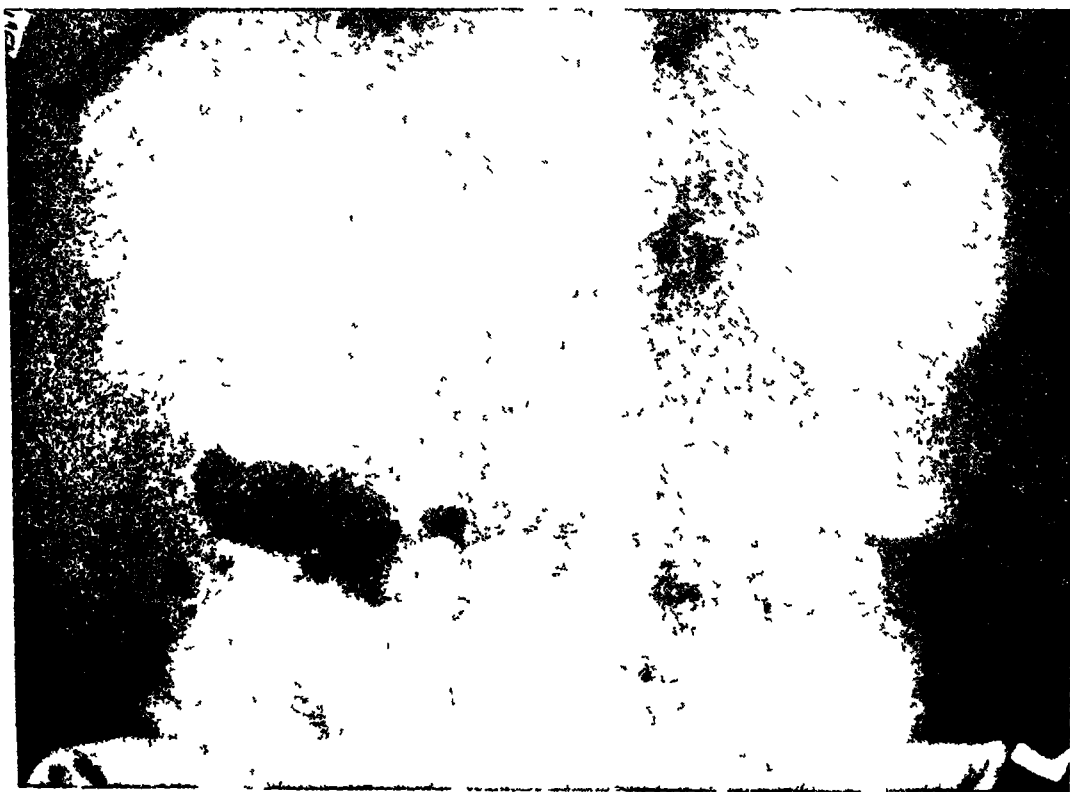


FIG 1 Thorotrast film. Cirrhosis of the liver shown by small size of organ and mottling, associated with splenomegaly.

(figure 2). The small opaque areas are the islands of liver tissue remaining in the fibrotic organ (figure 3). The diminished density of the liver shadow in other cases is due to the fact that the fibrous tissue is not as great in amount or forms a finer meshwork. Also, the number of functioning

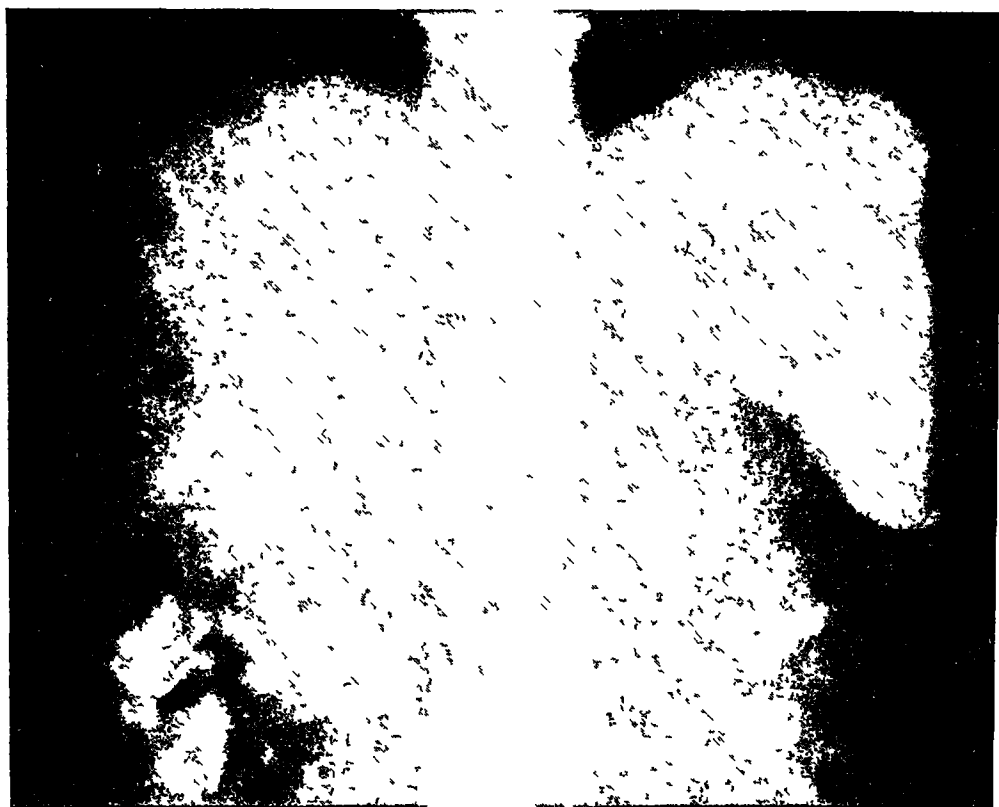


FIG 2 Thorotrast film Cirrhosis of the liver shown by greatly diminished density of liver shadow, associated with splenomegaly

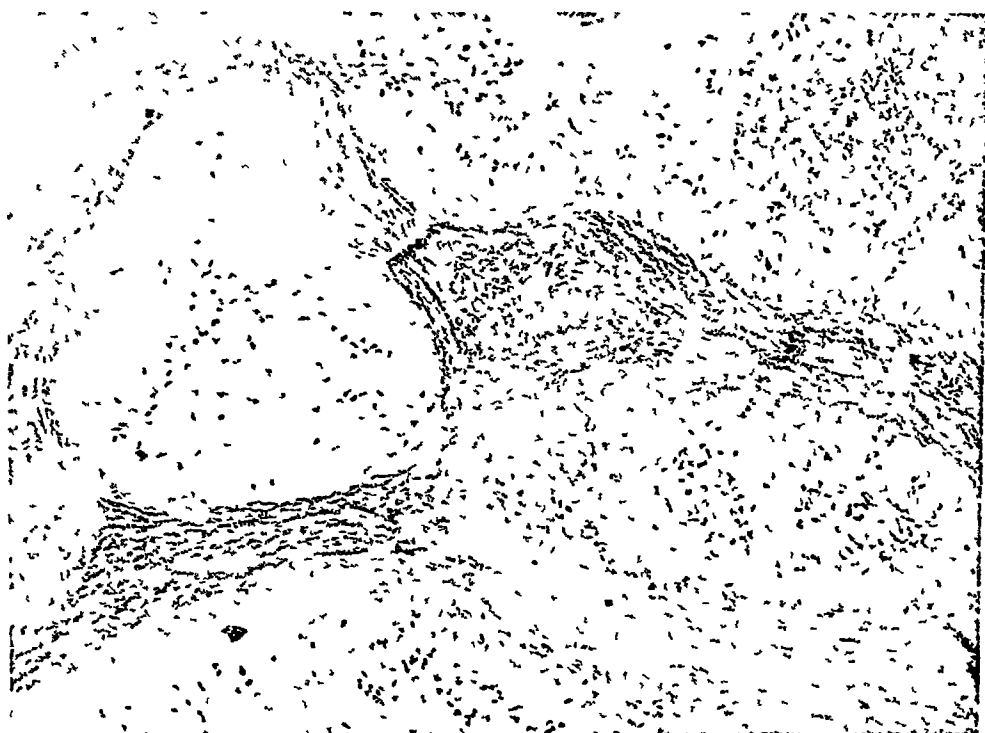


FIG 3 Photomicrograph of liver of case in figure 1, showing islands of liver tissue containing Thorotrast (black spots) surrounded by fibrous tissue devoid of Thorotrast

reticulo-endothelial cells in regenerated liver tissue may not be as great as in the original parenchyma. The spleen was shown to be moderately enlarged in eight of the cases, the density of the splenic shadow was normal. The presence of ascites was indicated in three cases by the presence of a space between the edge of the liver and the lateral wall of the trunk.

Metastatic Carcinoma of the Liver The presence of metastases in the liver was definitely determined in 10 cases. Necropsy was performed in five cases, and a biopsy was made in one other. The liver was enlarged in eight cases, greatly so in some. The spleen was apparently not enlarged in any of the cases. Metastatic nodules appear as circular, relatively non-opaque areas, often surrounded by a narrow rim of density more opaque than the normal intervening parenchyma (figure 4). The appearance is

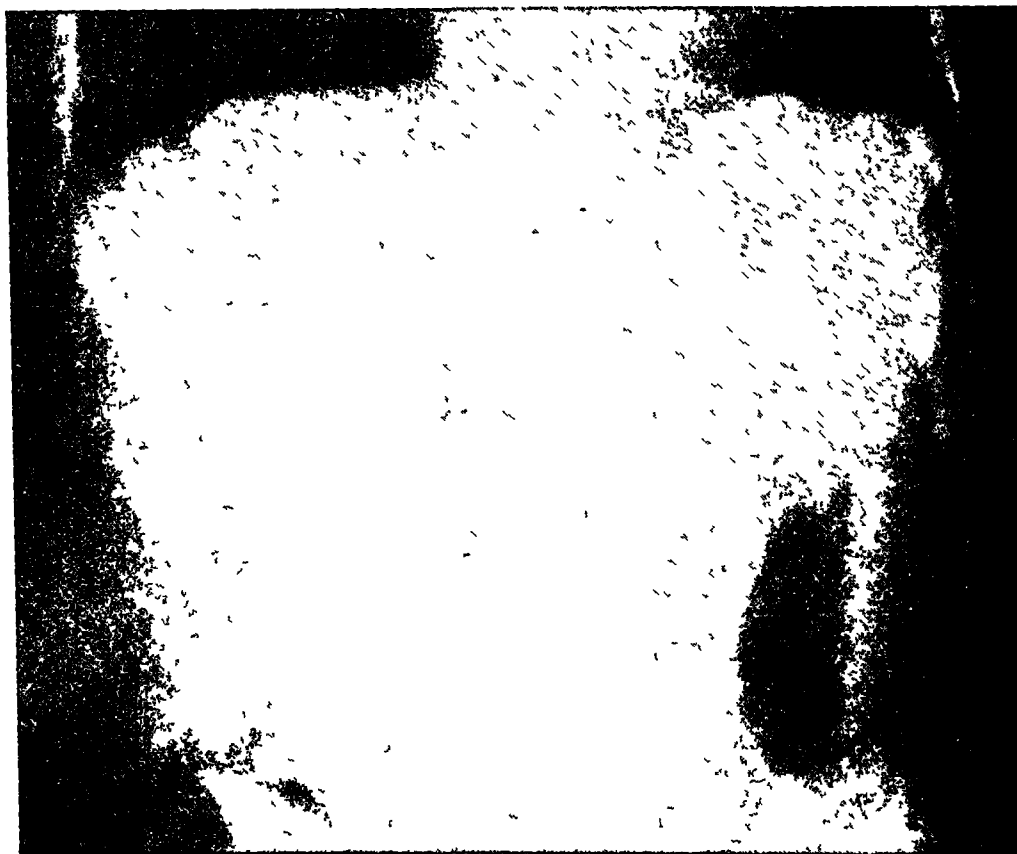


FIG 4 Thorotrast film. Metastatic carcinoma of liver shown by multiple, large and small, non-opaque, circular areas surrounded by a halo of increased opacity in a greatly enlarged organ.

due to the facts that the cancer tissue has a poorly developed reticulo-endothelial structure and that compression of the surrounding hepatic tissue causes local concentration of the reticulo-endothelial units. The method may be of great value in cases of abdominal carcinoma when the question of advisability of operation arises. In some of these cases the patients were saved from an operation which would have been of no avail.

Syphilis of the Liver Hepar lobatum could be diagnosed from the films alone in three cases. Necropsy was performed in one case. The blood Wassermann tests were strongly positive. This condition was indicated by enlargement, gross distortion and irregular, massive mottling of the liver shadow (figure 5)

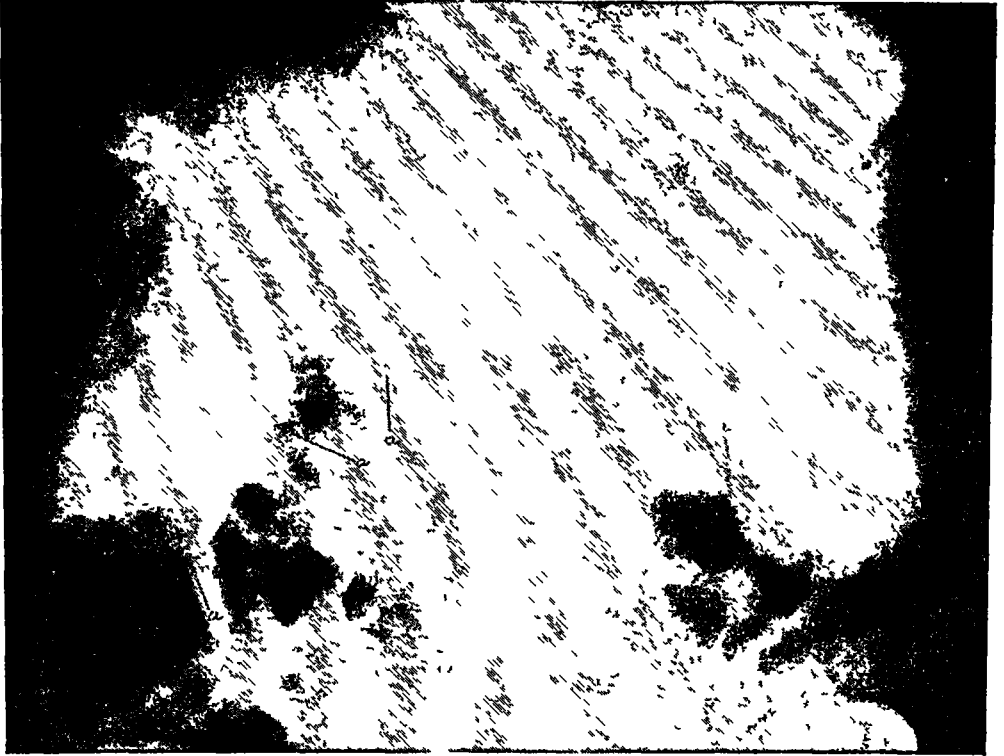


FIG 5 Thorotrast film. Syphilis of the liver (hepar lobatum) shown by greatly distorted, grossly nodular organ, associated with splenomegaly

Primary Tumor of the Liver This diagnosis was made in two cases before operation and biopsy. In one case clinicians had thought that a large mass in the right side of the abdomen was a tumor of the kidney. A large, irregular area of diminished density in the liver was noted in the film. The halo of greater density such as that which surrounds a metastatic nodule was not present.

CASES IN WHICH THE NATURE OF A MASS WAS DETERMINED

In seven cases a mass was felt in the abdomen, the nature of which was uncertain on physical diagnosis alone. Necropsy was performed in two cases and operation in two others. In one case an indefinite mass in the upper left quadrant was shown by the test to be the spleen. In another case a mass in the left flank was shown not to be the spleen, it turned out to be an abscess in the abdominal wall. In a child with tuberculous peritonitis two large masses in the upper abdomen were demonstrated to be the liver and

spleen The question of the nature of a mass in the upper right quadrant arose in a case in which it was found that the mass was not the liver, and in which operation revealed a high-lying appendiceal abscess In one case a large mass in the upper right quadrant was thought to be liver, but the visualization method showed the liver to be normal, and the mass proved to be carcinoma of the kidney In still another case a mass was felt in the upper abdomen which might have been the liver but which was proved by the visualization method not to be

CASES IN WHICH THE METHOD WAS CONFIRMATORY OF THE PHYSICAL DIAGNOSIS

In 13 cases enlargement of the liver and spleen, or both, was determined on physical examination The diagnoses made in these cases were acute catarrhal jaundice (1), Banti's disease (1), congestive heart failure (1), sickle cell anemia (2), purpura hemorrhagica (1), cured (?) leukemia (1), portal thrombosis (1), abdominal carcinoma (1), tuberculous lymphadenitis (1), no diagnosis (3) Necropsy was performed in two cases and splenectomy in one case The visualization method merely confirmed the physical diagnosis Structural alterations were not observed in the liver or spleen

CASES IN WHICH THE METHOD GAVE SUGGESTIVE INFORMATION WHEN COMPARED WITH THE CLINICAL PICTURE

In 11 cases the results alone of the method were not diagnostic but were of value when the clinical picture was considered in conjunction with them Biopsy was performed in three cases and operation in one case In another case the blood picture showed myeloid leukemia In the six remaining cases confirmation of the clinical diagnosis was not obtained Cirrhosis of the liver was diagnosed in five cases and proved by biopsy in two of them, metastatic carcinoma of the liver in two cases, hepatitis in one case which was proved by biopsy, myeloid leukemia in one case, ruptured spleen in one case in which operation had revealed a ruptured spleen that could not be removed, and primary carcinoma of the liver in one case In the case of myeloid leukemia the splenic shadow was notably less dense than normally, reduction in its size was easily determined in subsequent films following roentgen-ray therapy In the case of the ruptured spleen the normally sharp outline of the spleen was absent because of surrounding blood clots and gauze packing

CASES IN WHICH THE USE OF THE METHOD WAS VALUABLE IN RULING OUT LESIONS

There were 12 cases in the series in which it was deemed desirable to determine whether there were lesions of the liver or spleen Necropsy was performed in two of these cases and operation in two cases In nine of the cases the use of the method showed that metastatic carcinoma was not

present in the liver. In two of these, operation was performed because of the absence of hepatic metastases, but it was unavailing in both cases. Splenomegaly was ruled out in one case and splenic atrophy in another (a case of sickle cell anemia). Rupture of the spleen was suspected in the case of a girl who was run over by an automobile, the spleen was shown to be normal and the patient recovered without an operation. The procedure may be of great value in such cases, since one injection of 25 c c of Thorotrast followed by the making of a roentgenogram in four hours may tell the story.

CASES IN WHICH BY THE USE OF THIS METHOD THE POSITION OF THE RIGHT DIAPHRAGM WAS DEMONSTRATED

In two cases the right diaphragm appeared to be elevated in the flat roentgen-ray film, and Thorotrast was used to determine the position of the

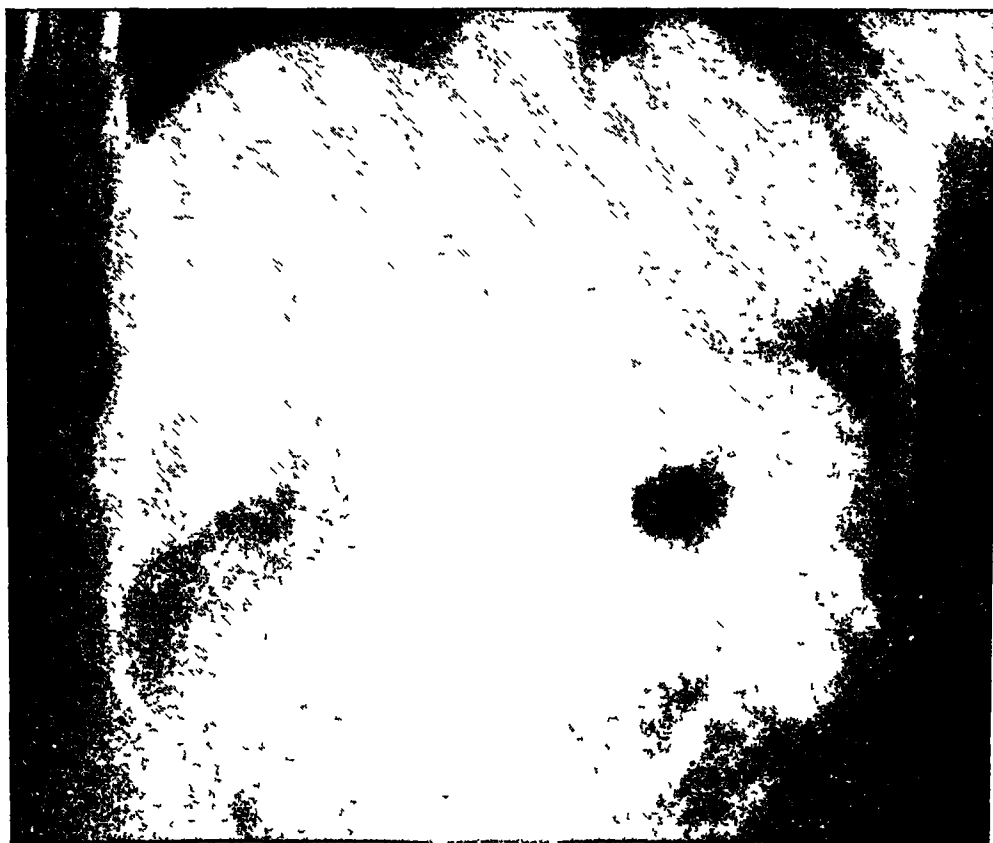


FIG 6 Thorotrast film showing eventration of right diaphragm with elevation of the liver
Flat x-ray film had given a definite impression of subphrenic abscess

diaphragm. In one case in which a subphrenic abscess was suspected eventration of the right diaphragm was demonstrated, the liver being merely elevated (figure 6), the fever was due to pelvic inflammation. In the other case it was shown that a lesion in the base of the right thoracic cage was the cause of the apparent elevation of the diaphragm.

CASES IN WHICH THE METHOD WAS EMPLOYED FOR SCIENTIFIC INFORMATION ONLY

In a case of xanthomatosis (Christian's disease) the procedure was carried out to determine whether the thorium dioxide would be taken up in the osseous lesions. It was not, and the spleen shadow was of normal density. A second case was one in which left hepatic lobectomy had been performed for amebic abscess. The film merely showed the absence of the left lobe, which apparently had not regenerated.

CASES IN WHICH THE METHOD WAS OF NO VALUE OR WAS CONFUSING

In eight cases the films made after the injection of Thorotrast did not give any information of value for diagnostic purposes. In one other case the method was not only of no value but it caused the wrong diagnosis to be made. The roentgenographic diagnosis was metastatic carcinoma of the liver. There were large vacuolated areas in the liver. The case proved at necropsy to be one of biliary cirrhosis due to obstruction of the common bile duct. Long-standing obstruction of the common duct causes dilatation of the bile ducts, and it is probable that the appearance of the liver in this case was caused by this. In other cases of obstructive jaundice we have noticed linear, branched spaces in the liver which we interpreted as due to dilated bile ducts. This appearance may be helpful in determining whether jaundice is due to obstruction of the common duct or to intrahepatic disease.

Accessory spleens were visualized in several of the 80 cases of this series.

CONDITIONS IN WHICH THE METHOD MAY BE OF VALUE

In the following conditions the procedure may yield valuable information: (1) any enlargement or alteration of the liver the cause of which is not known, (2) the presence of a mass in the abdomen which might be the liver or spleen but the nature of which is uncertain, (3) suspicion of the presence of metastases in the liver in cases of carcinoma of an abdominal viscus when the question of operability arises, (4) the question of an abscess in the liver as the cause of sepsis when no other focus can be located after exhaustive study, (5) the desire to follow the progress of intrahepatic or splenic disease (made possible by the slow elimination of the metal), (6) the possibility of traumatic rupture of the liver or spleen, (7) the question of the presence of free fluid in the abdomen, (8) uncertainty as to the location of the right diaphragm, and (9) the presence of splenomegaly the cause of which cannot be determined by other procedures (the least valuable indication for the method).

CONTRAINDICATIONS FOR THE METHOD

In view of the uncertainty of the effect of alpha radiation by thorium dioxide and the possibility of remote conversion of some of the substance to a more radioactive preparation, we suggest that for the present Thorotrast

be used only for patients who are subjects of a rapidly fatal disease. In our experience there have been practically no contraindications for the use of the method from other standpoints. In the case of patients who have lived for many months after the injections there have been no apparent ill effects. Even extremely ill patients have not appeared to be harmed by the procedure, although moribund patients should naturally not be subjected to it. It is possible that the use of the method may be inadvisable in hemorrhagic conditions. Simultaneous severe liver disease and renal insufficiency has been deduced by Kadrnka⁹ as a contraindication since this author thinks that most of the Thorotrast may be eliminated through the bile and urine, and its continuous presence in the circulatory blood might be detrimental. Whether the latter is true or not, one would hardly desire to make use of the procedure in patients with such a serious condition.

SUMMARY AND CONCLUSIONS

A new method of visualization of the liver and spleen developed mainly by Radt and Oka is described. This consists of the intravenous injection of thorium dioxide sol, from which the radio-opaque thorium dioxide is engulfed by the reticulo-endothelial cells of the body. Since these are most numerous in the liver and spleen these organs are visualized better than other parts of the body. This method is a laboratory procedure and should in no way replace clinical methods of diagnosis. It may not be harmless, but except for the possibility of radioactivity contraindications are negligible. Reactions are few and are not serious. Eighty cases have been studied by us and the value of the method in this series has been discussed. The results alone of this method were diagnostic of the nature of lesions of the liver in 24 cases. Evidence suggestive of the nature of the liver or splenic disease was obtained in 11 cases. The nature of an undiagnosed abdominal mass was determined in seven cases. Confirmation of enlargement of the liver or spleen or both was obtained in 13 cases. The method was valuable in ruling out lesions of the liver or spleen in 12 cases. Supplementary information was obtained from it in 11 cases, so that a working diagnosis at least could be made. The position of the diaphragm was established in two cases. The method was of scientific value only in two cases. No aid was obtained from it in eight cases, and in one case the wrong diagnosis was made on the basis of the method.

The following points may be determined by means of this method: (1) the presence of enlargement of the liver or spleen, (2) decision of the question of whether a mass in the upper abdomen is liver, spleen or something else, (3) the presence of metastases in the liver, (4) the presence of a primary tumor, cyst, or abscess in the liver, (5) in many cases the nature and extent of such intrahepatic diseases as cirrhosis and extensive scarring of the liver from syphilis, (6) the progress of such diseases of the liver, (7) the presence of free fluid in the abdomen, (8) the existence of such lesions of the spleen as tumor, infarct, abscess, fibrosis and leukemia, (9) the exist-

ence of rupture of the liver or spleen, (10) the position of the diaphragm, (11) the presence of accessory spleens, and (12) possibly the presence of obstruction of the common bile duct

As an adjunct to the previous methods of diagnosis the method is therefore of considerable value. Greater experience with it will reveal its true value, its finer points and its limitations.

The authors desire to express their appreciation to Major Virgil Heath Cornell, Curator of the Army Medical Museum, for the illustrations in this paper. Photographs of roentgen-ray films never do entire justice, however, to the details of the films, and the authors will be very glad to demonstrate the original films to those who may visit their clinic.

BIBLIOGRAPHY

- 1 EINHORN, M., and STILWART, W. H. On hepatography, *Med J. and Rec.*, 1927, cxxvi, 430-433
- 2 RADT, P. Eine Methode zur röntgenologischen Kontrastdarstellung von Milz und Leber, *Klin. Wchnschr.*, 1929, viii, 2128-2129
- 3 RADT, P. Über die körnige Ablagerung kolloider Farbstoffe in den Leberparenchymzellen von Kaninchen nach intravitaler Injektion (nach Versuchen mit Tusche und Eisen), *Ztschr. f. d. ges. exper. Med.*, 1930, lxi, 721-741
- 4 RADT, P. Zur röntgenologischen Kontrastdarstellung von Leber und Milz, *Verhandl. d. deutsch. Gesellsch. f. inn. Med., Kong.*, 1931, xlii, 443-451
- 5 RADT, P. Eine neue Methode zur röntgenologischen Sichtbarmachung von Leber und Milz durch Injektion eines Kontrastmittels (Hepato-Lienographie), *Med. Klin.*, 1930, xxvi, 1888-1891
- 6 OKA, M. Klinische Anwendung der "Lienographie" einer neuen Methode zur röntgenologischen Darstellung von Milz und Leber, *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1930, xl, 892-898
- 7 OKA, M. Eine neue Methode zur röntgenologischen Darstellung der Milz (Lienographie), *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1929, xl, 497-501
- 8 LIIPERT, T. Über die Verteilung des Thorium im Organismus nach Injektion von Thorotrast, *Wien. klin. Wchnschr.*, 1931, xlii, 1135-1136
- 9 KADRŇKA, S. Hepatosplenographie röntgenologische Darstellung des Parenchyms der Milz und Leber durch ein neues in die Blutbahn eingebrachtes kolloidales Kontrastmittel (Thorotrast), *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1931, xlii, 9-15
- 10 IRWIN, D. A. Experimental intravenous administration of colloidal thorium dioxide, *Canad. Med. Assoc. J.*, 1932, xxvii, 130-135
- 11 TRIPOLI, C. J., and HAAM, E. V. Effects of toxic and non-toxic doses of thorium dioxide in various animals, *Proc. Soc. Exp. Biol. and Med.*, 1932, xxix, 1053-1056
- 12 LAMBIN, P. Influence du dioxyde de thorium colloidal (thorotrast) sur la formule sanguine, *Compt. rend. Soc. de Biol.*, 1931, cviii, 264-266
- 13 POPPER, H. L., and KLEIN, E. Über Hepato-Lienographie, *München. med. Wchnschr.*, 1931, lxxviii, 1829-1830
- 14 SHIH, H. E., and JUNG, T. S. Thrombocytopenic purpura hemorrhagica produced experimentally with thorium, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxix, 243-245
- 15 HILF, A. Thorotrast und Infektion. Zur Frage der Blockade des retikulo-endothelialen Systems, *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1932, xlii, 330-334
- 16 HELF, A. Thorotrast und Infektionsabwehr, *Ztschr. f. d. ges. exper. Med.*, 1932, lxxxii, 218-222
- 17 HILF, A. Die Einwirkung der Thorotrast Injektion auf den Hamolysintiter des Blutes, *Klin. Wchnschr.*, 1932, xi, 463-464

- 18 VARA-LOPEZ, R, and THORBECK, K Rontgenologische Sichtbarmachung von Leber und Milz, Arch f klin Chir, 1932, clix, 236-244
- 19 RANDEKATH, E, and SCHLESINGER, M Experimentelle Untersuchungen uber die Wirkung des Thorotrastes (Heyden) im Tierkorper, Ztschr f d ges exper Med, 1931, lxxx, 245-260
- 20 OTELL, L S The reticulo-endothelial system and its relation to the roentgen study of the liver and spleen after intravenous administration of thorium dioxide solution, Radiology, 1932, xix, 148-156
- 21 Council on Pharmacy and Chemistry Thorotrast Preliminary report, Jr Am Med Assoc, 1932, xcix, 2183-2185
- 22 RADT, P Personal communication
- 23 BUNGELER, W, and KRAUTWIG, J Ist die Hepato-Lienographie mit Thorotrast eine unschädliche diagnostische Methode?, Klin Wchnschr, 1932, xi, 142-144
- 24 PFAHLER, G E The measurement of the liver by means of roentgen-rays based upon a study of 502 subjects, Am Jr Roentgenol, 1926, xvi, 558-563
- 25 L S O, W M Y Bulletin of Med Soc of the D C, Nov, 1931
- 26 EINHORN, M, STEWART, W H, and ILLICK, H E Experiences with uroselectan sodium, skiodan and thorotrast, Med Jr and Rec, 1931, cxxxiv, 56-59
- 27 STEWART, W H, EINHORN, M, and ILLICK, H E Hepatography and lienography following the injection of thorium dioxide sol (Thorotrast), Am Jr Roent and Rad Therapy, 1932, xxvii, 53-58
- 28 TRIPOLI, C J, HAAM, E, and LEHMAN, E B Roentgenographic visualization of the liver and spleen in the human a preliminary report, Am Jr Roent and Rad Therapy, 1932, xxvii, 265-266
- 29 YATER, W M, and OTELL, L S The differential diagnosis of diseases of the liver and spleen by the aid of roentgenography after the intravenous injection of Thorotrast (thorium dioxide sol), Am Jr Roent and Rad Therapy, 1933 (In press)

SOME ASPECTS OF CELL PHYSIOLOGY *

By W J V OSTERHOUT, *New York, N Y*

ALL AGREE that progress in medicine depends on accurate knowledge of the fundamental laws which govern all life processes. The study of these laws is the province of General Physiology, whose rise and development have been most gratifying, particularly since it has made use of the rapid advances of chemistry and physics.

In such studies it seems best to avoid the complexities of higher organisms and to attack first of all the simpler problems presented by single cells. This plan has met with a good deal of success, so that General Physiology is largely concerned with the study of the cell.

The significance of such studies for medicine is both theoretical and practical. Only through sound theory can medicine be saved from the blight of empiricism, the worst fate that could befall it. To theoretical studies we must always turn for clear insight into present problems, and for the inspiring vision of future conquests. Insofar as General Physiology succeeds in formulating a sound theory of living matter it will render to medicine a service of the utmost importance.

The application to medicine of the principles developed by General Physiology may not be immediate but in the majority of cases it is probable that it will eventually occur. I shall touch briefly on some instances of this in the course of my remarks.

Let me now call your attention to some cell studies which are of practical or theoretical interest.

Aside from pathogenic cells, the study of bacteria, of protozoa, and of other unicellular organisms is highly important. They not only reveal general laws which govern such organisms, but show apparent departures from these laws which are most suggestive in dealing with the pathogenic forms.

Such studies may yield specific methods of checking the parasite without injury to the host (as in chemotherapy and in radiation) and of controlling its dissemination outside of the body.

Observations on cells of the animal body are carried on in several ways.

A Observations of erythrocytes, lymphocytes and other isolated structures, help us to understand the functions of the blood and lymph in health and in disease. Matters of importance to medicine, such as the absorption and giving out of materials by the erythrocyte, and the process of phagocytosis have been successfully studied in this way.

B Certain eggs, especially those of cold-blooded animals, lend themselves readily to experiment and to microdissection which of late has made

* Read at the Montreal Meeting of the American College of Physicians, February 6, 1933.

From the Rockefeller Institute for Medical Research, New York, N Y

great advances From such material came the discovery of artificial parthenogenesis and much of our knowledge of the physical basis of heredity

C In transparent tissues, as the ear of the rabbit and the tail of the tadpole, the growth of cells can be followed under the microscope The behavior of lymphatics and of kidney cells can be directly observed in other animals

D Tissue cultures in vitro are most useful Observations on the artificial production of overgrowths in such cultures are a case in point, likewise the effect of growth-inhibiting substances obtained from adult organisms, and the effects of roentgen-rays Certain tissues of the kidney can be observed in this manner

Comparison of animal and plant cells yields general laws of fundamental importance An example is the conclusion that every living cell has a lipoidal surface It follows that substances soluble in lipid should be more readily absorbed by the cell surface (whether they pass from the surface into the body of the cell depends on other factors which have recently been pointed out in the "multiple partition coefficient" theory) This suggested a useful generalization regarding anesthesia, i e, that substances like ether and chloroform are good anesthetics because they are soluble in lipid materials and hence readily enter the cell surface

Another example is found in physiologically balanced solutions Certain animal and plant cells can live in distilled water but when we add sodium chloride it is toxic unless accompanied by the right amount of calcium A solution containing salts in such proportions that the toxic effects of each are counteracted by the other is called a physiologically balanced solution This explains the advantage of Ringer's solution over pure sodium chloride (physiological saline)

Physiologically balanced solutions are important for all kinds of cells Recognition of this has led to improved clinical methods Formerly the cerebrospinal canal was perfused with saline with disastrous results these disappeared when a balanced solution was used

The comparison of plant and animal cells has been useful in many ways Thus it has been found that plants may be far more sensitive than animals to substances produced in blood and other body fluids under disease conditions so that such changes may be readily detected by making appropriate tests on plants

I should like to mention one more example General Physiology is much concerned with respiration as a fundamental activity of living matter Accordingly a comparison of respiration in various types of cells becomes of interest It has been found that the cells of malignant tumors have a very different respiration from the normal cells which surround them Such a discovery is very significant

Although many of these experiments were performed on excised tissues or even on whole animals of a very simple sort, the point of view in all cases

was that of cell physiology and the object was to arrive at the fundamental laws which govern living matter in general

It should be emphasized that the application of physics and chemistry to medicine has come by way of General Physiology to a very large extent. Electrolytic dissociation and the Donnan equilibrium are good examples. The former is now too familiar to call for comment, the latter has found application in explaining the distribution of electrolytes in the case of erythrocytes and between blood and tissue fluids in edema.

It is not sufficient merely to study cells from the outside as in the experiments hitherto discussed. We need to get inside the cell in order to know what goes on there under a great variety of conditions. Ordinary cells are too small to permit this to a satisfactory degree for physiological purposes. But it is fortunately possible in the case of certain aquatic plants having cells larger than a pigeon's egg. Such cells can be kept alive for days while impaled on a capillary through which electric currents as well as various materials can be made to pass. This enables us to attack some fundamental problems which would otherwise be inaccessible. I shall deal more at length with this subject as it has not hitherto been placed directly before the medical public.

We employ two general methods which are made to check each other as far as possible.

- 1 Determination by chemical analysis of substances passing in or out of the cell and of processes occurring in its interior.

- 2 Measurement of the electrical changes which take place in the cell.

These methods have shown that these apparently simple cells are in reality exceedingly complex. They consist of a very thin layer of living matter (protoplasm) with a clear watery fluid inside (cell sap) and a firm cellulose wall outside. In spite of this simple structure they perform most astonishing feats.

We find, for example, that this thin layer of protoplasm (less than $1/250$ of an inch thick) excludes some substances but acts as a trap for others, such as potassium, which may become forty times as concentrated inside the cell as outside. Hence it commonly happens that the fluid inside the cell (i.e., the sap) is very different from the sea water in which it grows.

Strange to say, when some of this sap is applied to the outside of the cell it soon causes death. This suggests that when animal tissues are crushed or injured, so that the internal fluids of the cell escape and come in contact with the outside of other cells, they may have a deleterious action. Whether certain cases of wound shock can be explained in this way remains an open question. It is stated that when a muscle is crushed deleterious effects are produced in other parts of the body if the blood is allowed to circulate through the injured part, but not otherwise.

In seeking an explanation of this we found that the electrical state of the cell is completely altered when sap is applied to the outside, for it creates a considerable electric potential directed from the outside of the cell to the

inside This is in itself an interesting discovery for it shows that the very thin layer of protoplasm has an inner surface differing greatly from the outer This has been confirmed in other ways For example, when we apply certain toxic substances to the inner surface (injecting them through a capillary tube) the cell dies sooner than when they are applied to the outer surface (The introduction of the capillary does not account for this result for it is introduced into every cell, including the controls)

The electrical measurements are important in many ways They enable us to detect even slight injuries, to measure the degree of injury and of recovery from injury, and to follow the process of death step by step These methods are of especial value in the numerous cases where the cell retains its normal appearance after electrical tests show it to be dead

We may thus hope to substitute measurements and quantitative concepts for such vague and unsatisfactory expressions as normal vitality, injury, recovery, and death

If a small area of the cell be injured and we connect it electrically to an uninjured spot, we obtain the so-called "current of injury" Ordinarily the injured spot is negative but we have succeeded in making it positive and in thus reversing the "current of injury"

Certain of these plant cells behave electrically like muscle and nerve When a muscle or a nerve is stimulated an electrical disturbance passes along it Some plant cells give very similar electrical responses when stimulated electrically or by pressure, by reagents (including alcohol), or by change of temperature

Such plant cells are highly desirable for experimental work because they act like single fibers of nerve or muscle It is very difficult to obtain single nerve or muscle fibers for this purpose

Just as the heart muscle sets up spontaneous rhythmic electrical disturbances which we record by means of the electrocardiogram, so do these plant cells, and they yield photographic records which are sometimes very much like those of the heart The electrical disturbance which passes along the plant cell may perhaps be explained by the movement of potassium ions but this requires further investigation

Pursuing the analogy we may recall that the nervous mechanism does not always function properly and that the causes are not well understood It is therefore of interest that in plant cells certain reagents suppress for days at a time the normal electrical response after which irritability may be restored by changing the solutions bathing the cell

It is of interest, too, to find that we can also bridge over a dead spot on the plant cell by making a "salt bridge" consisting of cotton moistened with saline The electrical impulse will pass over this "salt bridge"

These electrical effects seem to depend on the presence of a non-aqueous layer at the surface of the watery protoplasm The smallest break in this layer causes death, i e., all the electrical effects disappear at once and substances can then pass in and out as they could not in a living cell The dead cell may for a time remain chemically about as it was when alive

This brings up the problem of the passage of substances into and out of the cell. In the living cell this exchange is restricted by the presence of a lipid layer since only those substances soluble in it can pass through.

It seems possible that the presence of this non-aqueous layer together with the production of carbon dioxide by the cell may explain the accumulation of such substances as potassium in the cell. Most cells contain a much higher concentration of potassium than exists in the external solution which bathes them. We can bring about a similar state of affairs in an "artificial cell" with a non-aqueous surface provided we supply carbon dioxide to the interior.

Problems of medication and of nutrition are intimately allied to this study, which seeks to determine the mechanism by which all substances pass in and out of the cell. Examples of this will at once occur to you, such as the proper administration of iodine and of iron which can be given in a variety of forms. The problems of excretion and of secretion, especially of the kidney, should here be mentioned.

These artificial cells throw a good deal of light on the relation between the cell and its environment. It was formerly thought that a growing cell comes into approximate equilibrium with the solution bathing it. We now see that when the cell grows without changing its chemical composition it is due to a "steady state" in which water and electrolytes enter the cell in the same ratio, just as they do in the artificial cell. This "steady state" may be very far from an equilibrium.

It is a very interesting fact that we can imitate some of the characteristic electrical effects of the cell by means of such artificial cells. This has a good deal of significance because electrical effects play a special rôle in the study of living matter. It is often said that life phenomena must always elude us because they involve so many variables and especially because we change these variables to an unknown degree whenever we subject the organism to experimental treatment. But electrical methods detect such small departures from the normal that we may hope to minimize such unknown disturbances. And the use of single cells and of artificial cells enables us to analyze the effect of the single variables to a remarkable degree. If such studies can yield measurements of all the variables we may be sure that the analytical resources of modern science can deal with them satisfactorily. This should provide a rational basis for biology and for medicine.

EDITORIALS

ENTRANCE REQUIREMENTS

WHETHER or not such thorough-going reorganization of the practice of medicine as is advocated in the majority report of the Committee on the Cost of Medical Care ever is put into effect, it is evident that the relationships of the physician to his colleagues, to the hospitals, and to an increasing number of social agencies are destined to become closer and will constitute a larger part of his professional life. The relatively simple rôle played by the physician when he cares for a sick person single-handed is becoming restricted to cases of minor illness. In an increasing number of instances the doctor must work in conjunction with nurses, with laboratory specialists, with roentgenologists, with administrative and professional staffs of hospitals, and with consultants. Very frequently he finds himself allied with public health officials and with social service agencies. He is called upon for statements concerning his patients by charitable institutions, by insurance companies, by industrial accident commissions, and by various courts of law. The results of his examinations often determine fitness for athletic sports, the question of employment or of discharge from employment, suitability for matrimony, and even whether a criminal is to be hanged or hospitalized.

The physician's professional value today is dependent not alone upon his own knowledge and skill, but upon his wisdom and unselfishness in the choice of his collaborators and his ability to work in harmony with them. The physician's social value depends likewise not solely upon the grade of his professional attainments but upon those qualities of heart, of judgment, and of integrity which induce him to accept the rôle of arbiter which society so frequently thrusts upon him and to show himself worthy of the trust.

In these relationships with patients, with colleagues and with society, there is inherent a demand for absolute trustworthiness. In no other field of human activity perhaps is a man so frequently called upon to make decisions which are contrary to his own economic interests, or which involve the assumption of grave responsibilities, or which lead to the loss of sorely needed rest. If, then, the evolution of the medical profession is to increase still further the organization for medical care and integrate this organization even more closely with all the other social agencies of the community, how vital it is to the future of medicine that those admitted to its ranks should measure up well, not only to the intellectual demands which they must meet, but to the demands for character.

The medical schools, through their entrance requirements, hold in their hands the power to raise or to lower the standards of the medical profession of the future. The responsibility is a great one. It will not be met if admission to the medical school is granted on scholastic attainments alone.

It is not difficult to set up criteria of intellectual accomplishments which will eliminate most of the intellectually unfit, but it is exceptionally difficult to determine who will and who will not be worthy of trust. The selection of men for character as well as for ability is, however, a recognized necessity in many types of human organizations. This principle of selection should be openly adopted by our medical schools.

THE INFLUENCE OF THE ADRENAL CORTEX UPON SALT AND WATER METABOLISM

THE DEVELOPMENT of knowledge of the function of each of the various glands of internal secretion frequently runs a curiously similar course. Research into the nature of the rôle of such a gland in the body economy is usually followed along one of two lines which are well defined. The first involves the study of the effects of deficit, such as may be obtained by complete or partial removal of the organ in question, leaving the rest of the body, as far as possible, intact and uninjured. The second method consists in attempts to produce effects from replacement of the secretion in question either by gland transplant or by the elaboration of an active extract of the characteristic principle. Use of such a potent preparation will either make up the deficit produced by removal of the gland itself, or, if given in excess, may enable the investigator to observe the physiological effects of hyperfunction.

Speculation as to the possible function of a hormone whose action is not understood usually proceeds along one of two paths. The one considers the hormone to be an essential link in some more or less clearly defined metabolic activity, while the other is based on the theory that it has some detoxifying action. The second idea has been advanced to explain, at one time or another, the action of most of the known hormonal secretions, particularly during the period before a satisfactory preparation of the hormone itself has been isolated. The name *pituitary* suggests the ancient theory of its function—to rid the body of effete materials by way of the nasal secretions. The idea has recurred frequently, particularly as regards the secretion of the pancreas, that of the thyroid gland, and, most recently, regarding that of the parathyroids. As each hormone is isolated in a form sufficiently pure to enable satisfactory experimentation to be carried out without confusing side reactions due to the presence of impurities, the theory of detoxification in each case disappears. Since studies have been possible with the aid of parathormone, articles on guanidine tetany have disappeared from scientific periodicals.

The history of the study of the function of the adrenal cortex furnishes still another case in point. Until very recently the arguments of the proponents of a "detoxification" theory about evenly balanced those of investigators who considered that it fulfilled a specific metabolic function. Indeed, confusion has been so great that previous interpretations of the

most obvious clew were based on the theory of detoxification, which has proved to be quite erroneous. It has been known for nearly seventy-five years that removal of the adrenals, in the absence of accessory tissue, eventually causes death, the labors of a large group of investigators during the past two decades have proved that the "vital" portion of the gland is the cortex. Over the same period of time the observation has been made repeatedly that the injection of fluids containing salt will maintain the lives of animals deprived of their adrenals for periods several times as long as the survival periods of untreated controls. Stewart and Rogoff (1924), and Banting and Garms (1926) have reported convincing experiments on dogs. Marshall and Davis (1916) and Corey (1928) have reported similar results in cats. Marine and Baumann (1927) found that not only physiologic saline solution or Ringer's solution, but sodium acetate as well, by daily intraperitoneal injection, were effective in prolonging the lives of adrenalectomized cats. Sodium glycerophosphate was less effective, but much more potent than glucose. They concluded that the sodium ion rather than the chloride ion was responsible for the favorable effect. Baumann and Kurland have particularly stressed the loss of chloride and of sodium from the blood plasma of the suprarenalectomized cat. Of the authors advocating the use of sodium chloride in the treatment of Addison's disease, Rogoff especially has stressed the importance of injections of physiological saline solution as an "indispensable aid" in the treatment of the acute manifestations, which are certainly very closely allied to the experimentally produced insufficiency. Nearly all of these observers, however, explained their findings on the theory of "detoxification"—a flushing out of poisons formed in the body as a result of normal or of perverted metabolism. The idea dies hard that some of the products of normal metabolism may be toxic and must be dealt with by a special means. It is by no means impossible that such may yet turn out to be the case, and that endocrine secretions may be involved, but each time the theory has been postulated in the past it has been disproved.

The similarity between the clinical picture of the crisis in Addison's disease, of adrenal insufficiency in the experimental animal, and of the general condition of "shock" is very striking. In the experimental adrenal insufficiency, blood concentration, loss of body weight and dehydration occur. Loeb has recently shown that a characteristic loss of sodium occurs from the blood and extracellular fluids, and that the loss takes place through the kidneys. Loss is possible through the gastrointestinal tract as in the shock produced by cholera or intestinal obstruction, as well as in the fluids lost into the tissues in traumatic shock, but neither of these routes is important in producing the loss of sodium, the dehydration, and the concentration of the blood in adrenal insufficiency. When injections of the cortical hormone are made into such an animal, the kidney threshold for sodium is again raised to the normal level, and the plasma electrolytes resume their normal concentrations. Loeb advances the opinion that the cortical hor-

mone regulates sodium metabolism just as parathormone regulates that of calcium

The discovery of this regulation of sodium metabolism is of great significance. Investigation of the behavior of the inorganic constituents of the body fluids in recent years, particularly by Gamble, has indicated that the electrolyte concentration controls the amounts of fluids which the body contains. Loss of electrolytes inevitably produces loss of fluid as well. This must necessarily follow from the obvious conception that a stable osmotic pressure, as well as a stable temperature and acidity, is essential to the integrity of the living organism. Since it has been shown that the concentration of total base regulates the total concentration of electrolytes—which in its turn regulates the osmotic pressure—and since sodium accounts for 85 to 90 per cent of the total base of the blood plasma and extracellular water, the predominant rôle of the adrenal cortex in the regulation of the metabolism of salt and water, by reason of its control of the excretion of sodium can readily be appreciated. An interesting corollary to the effect of the cortical hormone upon salt and water metabolism is the fact that the hormone is powerless to relieve adrenal insufficiency in the experimental animal if sodium chloride or some other sodium salt is not provided at the same time in adequate amounts. Hetzel has shown that the plasma volume may drop about 50 per cent with the loss of sodium and chloride in the urine in adrenal insufficiency. The volume may double, on the other hand, if large amounts of the hormone are given intravenously, together with ample salt, but the result is not lasting. Other mechanisms appear to be able to counteract such an effect.

Recent studies have made much clearer the importance of adrenalin, the hormone of the adrenal medulla, in carbohydrate metabolism, the control of which it appears to share with insulin. The uncovering of the rôle which the other portion of the adrenal gland plays in the metabolism of salt and water indicates the fundamental importance of this organ in quite a different phase of the body economy. One or both of these functions may or may not have an intimate bearing on the less obvious and more subtle effects of adrenal dysfunction which clinical observations indicate exist in sex development and growth, and in the interaction of the other endocrine glands.

GEORGE A. HARROP

REVIEWS

Case Studies in the Psychopathology of Crime By BEN KARPMAN, M D , Psychotherapist, St Elizabeth's Hospital, Professor of Psychiatry, School of Medicine, Howard University, Washington, D C 1042 pages The Mimeoform Press, Washington, D C 1933 Price, \$12 00

This massive volume is the record of five cases seen by the author in Howard Hall, the Department for Criminal Insane at the federal psychiatric hospital under the superintendentship of William A White, M D , F A C P , who has inspired much of the progress in the scientific treatment of criminals

As the author states in his preface "No apology is needed at present for any attempt to elucidate the problem of crime Of all social problems it is undoubtedly the most pressing, of all the influences, the most demoralizing one No economic expression of its cost, however high, can ever depict its present and far-reaching effect upon the community The social, ethical, and above all individual psychic effects of crime go to the root of communal life and threaten it with destruction Cancer-like it encroaches upon healthy living, normally functioning members, thriving at their expense, absorbing everything that may be useful to the social body but giving nothing in return "

This volume presents an excellent example of the ideal case history as presented from the patient's viewpoint supplemented by the opinion of his associates Each history is presented in a scientific and systematic manner beginning with the official record which contains a brief statement of the patient's crime, his family history, his personal history, with detailed statement of his present illness, followed by the results of the psychiatric examination, physical findings, laboratory findings, and progress while in the hospital

As the author states "Many books written by criminals themselves while giving detailed accounts of how crimes are committed leave almost entirely unanswered the question of why the crime is committed Routine psychiatric histories are in most cases quite unreliable and give only misleading pictures of the case "

As a method of bringing out the intricacies of the psychogenetic factors in criminal behavior, the author has had the patient present in autobiographical form, sometimes in a rather boring manner, his own history Psychoanalysis in any of its forms has been used only to a limited degree, and the author is apparently not arguing for psychoanalysis although he is an accredited practitioner of this art

As the reviewer spent hours wading through ream upon ream, he was impressed with the scientific value of this type of case history He could not recommend the book as light reading, except for its aphrodisiac effect, especially the lurid details of Case No 3 In spite of the fact that details are not missing, the reader is not offended by the vividness of the experiences One might at first criticize the voluminousness of these histories, but further consideration convinces the reviewer that the object of the author is only gained by such detail As he himself states in the opening paragraph of the first case "the general type of information ordinarily obtained from a patient gives one but little clue to the vast pathology that may be involved "

No matter what the reader's theory may be as to the cause of crime, he will find within this volume a great deal of enlightenment, and he will be impressed with the need for more careful consideration of the psychogenetic factors in everyday life "The criminal," after all, represents a member of society who has been caught The internist meets in his practice every day potential criminals who through human interest and understanding may be prevented from anti-social behavior Too much cannot be said in favor of careful consideration of the psychogenetic factors Dr

Karpman has not only contributed a valuable treatise to the as yet rather limited bibliography on the genetics of crime, but he has also contributed five case histories which will give any sincere physician a better understanding of human behavior. And since medical science has been asked to contribute its part to the solution of crime, it is well that more members of the profession become acquainted with the painstaking work that is being done by their confrères in this field.

J. L. MCCARTNEY, M.D., F.A.C.P.,
Director, Classification Clinic,
Elmira Reformatory, Elmira, N. Y.

The Tides of Life The Endocrine Glands in Bodily Adjustment By R. G. HOSKINS, Ph.D., M.D., Director of Research, Memorial Foundation for Neuro-Endocrine Research, Research Associate in Physiology, Harvard Medical School. 352 pages. W. W. Norton and Company, Inc., New York. 1933. Price, \$3.50.

The author is a noted physiologist who has spent most of his professional life in research in the field of the internal secretions. His own work and interest and his editorial activities have given him a very broad knowledge of the tremendous literature of the subject.

It was no easy task that he set for himself, that of presenting in a semi-popular style "the more significant aspects of endocrinology as known today" without indulging too freely in its romantic temptations, but the author has succeeded very well indeed in giving a lucid, reasonably concise and sufficiently conservative exposition of his subject.

As might be expected he seems happier in his discussion of the laboratory features than in the clinical portions of the book and if certain critics take exception to the rather frequent inclusion in some chapters of "interesting speculations" they must admit that the author is usually careful to label them as such.

The book may be highly recommended to the audience for whom it is evidently intended, namely practitioners of medicine, students and intelligent laymen with an interest in biology.

T. P. S.

Anatomy of the Brain and Spinal Cord By WILLIAM W. LOONEY, A.B., M.D. Second Edition. F. A. Davis Company, Philadelphia. 1932. Price, \$3.50.

This book is a concise description of the nervous system. The preface leads one to assume that it has been written as a text for medical students (the preface of the first edition is not included in this printing). If this assumption is correct it carries with it an obligation to develop the subject in a manner which is understandable to a beginner in the subject. To quote Dr. Looney "It is suggested that the student familiarize himself with the external and internal configurations of the brain, as well as of the spinal cord, before undertaking the study of the tracts, as this will greatly facilitate his comprehension of them" (page 83). Then follows a systematic description of the long tracts of the cord throughout their entire course, both spinal and cranial including many references to associated tracts and centers of the brain, none of which have received the slightest previous attention on the part of the author.

The meninges and blood supply are handled with the same disregard of the structures with which they are associated. The medulla oblongata, pons and midbrain are discussed in the order named. Finally, after a somewhat didactic discussion of the cranial nerves there follows a description of the cerebellum and forebrain. Throughout this narrative the most liberal reference is made to hitherto undescribed parts of the brain. Surely with a subject as inherently complex as that of neuro-anatomy such an added handicap as this method imposes has little to recommend it.

The classification of receptors on the basis of their relation to the three primary germ layers appears to lack substantiation in fact. Neither exteroceptors, proprioceptors, nor interoceptors are confined to any one germ layer. It seems almost inconceivable that such an error as this could find its way into a textbook.

In his anatomical description the author is both concise and clear, but there is a conspicuous lack of reference to the phylogenetic relationships existing in the nervous system, a subject which is assuming more and more significance in medicine as is shown by the greater resistance to pathological processes exhibited by the more primitive structures as contrasted with the newer parts. The author has stressed the function of the various structures in a convincing manner and his brief explanation of the phenomenon of nerve degeneration is a happy inclusion which is seldom encountered in works of this kind.

A useful general bibliography is appended to the text.

C L D

The Practitioner's Library of Medicine and Surgery Supervising Editor GEORGE BLUMER, M A (Yale), M D, F A C P, David P. Smith Clinical Professor of Medicine, Yale University School of Medicine, Consulting Physician to the New Haven Hospital. Volume IV *Nontraumatic Surgery* Associate Editor THEODORE S. MOISE, JR., B A, M D, Surgeon to the Eastern Maine General Hospital, Bangor, Maine. xlviii + 1146 pages, 335 illustrations. D. Appleton and Company, New York and London. 1933. Price, \$10.00.

The first three volumes of *The Practitioner's Library of Medicine and Surgery* dealt, respectively, with Anatomy and Physiology as Applied to Practical Medicine, The Technic of Physical and Laboratory Examination in Clinical Medicine, and Practice of Medicine. The present volume (*IV, Nontraumatic Surgery*) contains sections contributed by twenty writers most of whom have been chosen because of special interest and experience in the fields which they have been asked to treat. Much inequality in completeness of presentation is evident in passing from one section to another, for instance, surgery of the pericardium and heart together occupy 57 pages while carcinoma of the prostate is allotted about 2. When evidences of compression in order to include such a wide field are so obvious, the wisdom of devoting space to surgical technic may well be questioned. Operative procedures are not to be learned from books. As a general reference work, the present volume will serve its purpose well. If it could have been developed as two volumes it would have been still more useful. The typography is excellent and the illustrations are well reproduced. Since this volume is of greater interest to the surgeon than to the internist, fuller description cannot be given here.

C V W

Endocrine Medicine By WILLIAM ENGELBACH, M D, F A C P, B S, M S, D Sc Professor of Clinical Medicine, St. Louis University School of Medicine, 1911-24, Physician-in-Chief, St. John's Hospital, 1909-24, Member of Staff St. Louis, City, Jewish, Baptist Sanitarium, and Maternity Hospitals, President of Association for Study of Internal Secretions, 1922-23, President of the St. Louis Medical Society, 1918, Fellow of The American Medical Association and American College of Physicians, Member Missouri, Illinois, New York and Southern Medical Societies with a Foreword by LEWELLYS F. BARKER Professor Emeritus of Medicine, The Johns Hopkins University School of Medicine. Volume I, *General Considerations*, xxviii + 460 pages, 139 illustrations, Volume II, *The Infantile Endocrinopathies, The Juvenile Endocrinopathies*, xviii + 473 pages, 109 illustrations. Volume III, *The Adolescent Endocrinopathies, The Adult Endocrinopathies*, xxiv + 862 pages, 255 illustrations, Volume IV *Bibli-*

ography, Index, 117 pages Charles C Thomas, Springfield, Illinois 1932
Price, \$35 00 for four volumes

Review of *Endocrine Medicine* has been delayed awaiting the appearance of the fourth volume containing the Bibliography and the Index. During this interval came word of the death of the author. To his enthusiasm for his chosen field, his industry and thoroughness this work has become a very fitting testimonial. What better memorial can be conceived than that which makes it possible for a teacher, clinician, and investigator to record in permanent form the results of his endeavors and the conclusions derived from mature experience! Thus, much which would otherwise have perished with the man is preserved to be of use to others and to augment the totality of knowledge.

In the first volume of *Endocrine Medicine* are presented the essential general considerations such as gross and microscopical organology, and the physiology of the endocrine systems. The etiology of disturbances of function of the endocrine glands is then discussed from both extrinsic and intrinsic standpoints, and these chapters are followed by a series giving first the diagnostic procedures in the investigation of the endocrine state of the patient, and then a discussion of the endocrine reactions. This volume is concluded with chapters on the relation of the endocrinopathies to general medicine and to public health. The second volume is devoted to the infantile and juvenile endocrinopathies. Under the first division thyroid, hypophyseal, biglandular, gonadal, and parathyroid disorders are considered in the order named. For the juvenile endocrinopathies the order of presentation is much the same, the parathyroid section being replaced by one on the thymic syndromes. The third volume deals similarly with adolescent and adult endocrinopathies, 298 pages being devoted to the former and 563 to the latter. The fourth volume gives an extensive bibliography, by chapters, with alphabetical listing under each. This fills 51 pages, and is followed by detailed name and subject indexes.

Endocrine Medicine is the product of a courageous and successful attempt to put in orderly arrangement the content of this highly labile subject. It establishes routine procedures for investigating and evaluating the endocrine state of the individual. Throughout, it is very well illustrated and is replete with charts and tables for differential diagnosis. More than 2000 clinical case reports are utilized, many of them of patients who had been observed for more than ten years. Therapeutic procedures are discussed with a rational scientific conservatism which, too often, has been found wanting in this particular field. This set should have a place in every medical library, but it is of more than reference value. It gives the entire essential subject matter for the pediatrician or internist who is concerned especially in this field, and for all others engaged in medical practice of any description it provides a wealth of informative and stimulating material. Even with the lesser manifestations of endocrinopathy, there are certain inherent predispositions to diseases of other systems, knowledge of which places the practitioner in a strategic position in respect to differential diagnosis.

C V W

Acidosis and Alkalosis By STANLEY GRAHAM, M D, F R F P S, Leonard Gow Lecturer on the Medical Diseases of Infancy and Childhood, University of Glasgow, and NATH MORRIS, M D, B Sc, D P H, F R F P S, Lecturer in Biochemistry, University of Glasgow. Ed. 1 xi + 203, 13 × 19 cm. William Wood and Company, Baltimore, Md. 1933. Price, \$2 75.

In this small volume the authors have attempted to present a general survey of the fundamental concepts of acid-base equilibria as these are related to acidosis and alkalosis. This has been accomplished, and the mode of presentation is adopted to the understanding of the clinical reader.

The subject matter of the book falls naturally under three general headings. The first section deals with the reaction of the blood, the physical chemistry of carbonic acid and a survey and explanation of the terms to be employed in the following expositions. The second portion treats of the clinical applications of changes in acid-base equilibria in various types of disease. Diabetes, nephritis, gastro-enteritis, cyclical vomiting, ketosis, salicylate poisoning, anesthesia and other topics are discussed. The third part is in the nature of an appendix and embraces the ketogenic value of foods, the preparation of reagents and a discussion of normal and molar solutions.

In covering so wide a field the authors have been unable to treat these subjects with thoroughness or completeness. Nevertheless in each instance the important and often the most recent information on the subject has been satisfactorily presented.

It is to be regretted that throughout the volume, in chemical equations indicating the dissociation of electrolytes, the ions formed do not show their respective charges. The table on page 8 is antiquated. It is now generally conceded among physical chemists that strong electrolytes are more than 99.9 per cent dissociated in aqueous solution. In the chapter on the reaction of the blood nothing is mentioned concerning the nice difference in pH between arterial and venous blood.

On the whole the purpose of the authors as set forth in the preface, namely, to present the subjects of acidosis and alkalosis and their medical importance in a manner that will interest the clinician has been well fulfilled.

J C K, JR

Modern Aspects of Gastro-Enterology By M A ARAFA, M R C P (Lond), Medical Assistant to Guy's Hospital, London, Medical Tutor to the Egyptian University and formerly senior medical registrar to Kasr-El-Ainy Hospital, Cairo xvii + 374 pages, 17 X 23 cm William Wood and Company, Baltimore 1933 Price, \$8.25

The title, *Modern Aspects of Gastro-Enterology*, is in itself inviting, the compactness of the volume and the arrangement of material will appeal to those who have long wished for a brief treatise on Gastro-Enterology.

Though the author has chosen for discussion only some of the more important diseases of the gastrointestinal tract he has dealt with most of the other conditions in the sections on general methods of investigation and differential diagnosis. Nevertheless many subjects have received only brief mention in order to keep the size of the book within limits. The roentgen-ray plates illustrating certain of the commoner gastrointestinal abnormalities are excellent.

It is interesting that chronic gastritis, a disease the existence of which was disputed a few years ago, is accorded a prominent place in this volume. In view of recent advances in gastro-enterology it is fair to state that chronic gastritis deserves increasing attention and that the author has done wisely in recognizing this fact.

The author is cautious in accepting new forms of treatment and he admits frankly that such modern methods of therapy as Fogelson's mucin and Glassner's pepsin have not passed the experimental stage. The decided denunciation of the ambulatory treatment of peptic ulcer will come as a surprise to many of us although there can be no question that rest is of the greatest importance in the treatment of this condition. The author predicts that "the day is not far distant when we shall realize that, if adequate medical treatment of peptic ulcer fails and if there is a real indication for operation, anything short of gastrectomy is unlikely to result in a permanent cure of the patient."

The chapters on The Pancreas, The Simulation of Gastrointestinal Diseases and Practical Dietetics are excellent. The latter two chapters are especially good since they give the student information which is too little stressed in the ordinary medical curriculum.

Perhaps the fact that the author's experience has been obtained chiefly in England and Egypt accounts for his failure to refer to some of the more prominent names in American Gastro-Enterology. The index of subjects, too, could be more complete, and certain diseases, such as cancer of the stomach, deserve a fuller discussion. The influence of Hurst, with whose clinic the author was associated, is evident in many of the opinions expressed.

The book may be recommended as a valuable addition to the library of practitioners and of students of gastro-enterology.

S M

COLLEGE NEWS NOTES

The New York Academy of Medicine will conduct its Sixth Annual Graduate Fortnight, October 23 to November 3, 1933. The two weeks will be devoted to metabolic diseases. Many clinics will be given by Fellows of the College. Dr. Walter W. Palmer, New York City; Dr. Emanuel Libman, New York City, and Dr. Priscilla White, Boston, are Fellows of the College who will address evening sessions.

Acknowledgment has been made in these columns from time to time of gifts to the College Library of publications by members. The College has been engaged for some time in the collection of a library of books of which Fellows and Associates are the authors. The Library is maintained as a memorial to its members. Its usefulness and value, as well as sentiment, will increase as the College grows older. Recent contributions by the authors include:

Dr. O. H. Perry Pepper (Fellow), Philadelphia, Pa., and Dr. David L. Farley, Philadelphia, Pa.—1 book, "Practical Hematological Diagnosis",

Dr. John Favill (Fellow), Chicago, Ill.—1 book, "Outline of the Cranial Nerves",

Dr. H. M. Margolis (Associate), Pittsburgh, Pa.—1 book, "Conquering Arthritis",

Dr. William Gerry Morgan (Fellow), Washington, D. C.—2 reprints,

Dr. Julius P. Dworetzky (Fellow), Liberty, N. Y.—1 reprint,

Major Leon A. Fox (Fellow), Medical Corps, U. S. Army—1 reprint,

Dr. Frederick R. Taylor (Fellow), High Point, N. C.—4 reprints,

Dr. Philip B. Matz (Fellow), U. S. Veterans' Bureau—1 reprint,

Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint,

Dr. William A. Groat (Fellow), Syracuse, N. Y.—2 reprints,

Dr. M. D. Levy (Fellow), Houston, Tex.—17 reprints,

Dr. W. R. Brooksher, Jr. (Fellow), Fort Smith, Ark.—2 reprints,

Dr. George W. Parson (Associate), Texarkana, Tex.—4 reprints

Dr. Eugene E. Murphey (Fellow), Augusta, Ga., retired as Chairman of the Augusta Board of Health on June 9th, after serving for more than twenty-five years. Dr. Murphey is credited as being the first health officer in Georgia to recommend and use tuberculin tests for dairy cattle, establishment of mosquito control, chlorination of the city's water supply, establishment of municipal laboratory, establishment of routine inspection of school children, and the practical elimination of rabies.

At the meeting of the National Tuberculosis Association at Toronto during June, Dr. Stuart Pritchard (Fellow), Battle Creek, Mich., was elected President and Dr. H. R. Landis (Fellow), Philadelphia, Pa., Second Vice-President. Dr. Kennon Dunham (Fellow), Cincinnati, Ohio; Dr. Willard B. Soper (Fellow), New Haven, Conn.; Dr. James J. Waring (Fellow), Denver, Colo., and Dr. John H. Peck (Fellow), Des Moines, Iowa, were elected members of the Executive Committee.

The Fourteenth Annual International Medical Postgraduate Course given at Carlsbad this year with special reference to balneology and balneotherapy took place from September 10th to 16th. Lectures were delivered on the most important medical topics by eminent clinicians and surgeons of various countries. The United States of America was represented by Professor Max Einhorn (Fellow), New York City, and Professor Carl F. Cori, of St. Louis, Mo., who both addressed the Congress.

The Georgia State Medical Association, Emory University School of Medicine and the Georgia State Board of Health, in cooperation, offered a series of summer extension courses throughout the State during the summer. Dr. Cyrus W. Strickler (Fellow), Dr. James E. Paullin, Jr. (Fellow), and Dr. Stewart R. Roberts (Fellow), all of Atlanta, gave the courses in medicine.

Dr. Mary O'Malley (Fellow), Washington, D. C., was installed as President of the Medical Women's National Association at its meeting in Milwaukee during June.

Under the presidency of Dr. Seale Harris (Fellow), Birmingham, Ala., the Chattahoochee Valley Medical Association held its Thirty-Third Annual Session at Albany, Ga., July 11th to 12th. A number of the Fellows of the College contributed to the program.

Dr. Ernest S. duBay (Fellow), San Francisco, Calif., and Dr. Mark L. Gerstle, Jr. (Associate), San Francisco, Calif., were recently advanced to the rank of Associate Clinical Professor of Medicine and Assistant Clinical Professor of Neurology, respectively, at the University of California Medical School.

Dr. Hugh S. Cumming (Fellow), Washington, D. C., Surgeon General of the U. S. Public Health Service, was the recipient of the honorary degree of Doctor of Laws from Yale University.

Dr. William B. Castle (Fellow), Boston, Mass., Assistant Professor of Medicine at Harvard University Medical School and the 1933 recipient of the John Phillips Memorial Prize given by the American College of Physicians, recently received the honorary degree of Master of Science from Yale University.

Dr. Robert O. Brown (Fellow), Santa Fe, N. M., has been elected President of the New Mexico Tuberculosis Association.

Dr. John A. Toomey (Fellow), Cleveland, Ohio, has been advanced to Associate Professor of Pediatrics at the Western Reserve University School of Medicine, Cleveland.

A portrait of Dr. Henry A. Christian (Fellow), Boston, Mass., was presented to the Peter Bent Brigham Hospital at a dinner in May. Dr. Christian is Professor of the Theory and Practice of Physics and Physician-in-Chief to the Peter Bent Brigham Hospital.

Dr. Joseph F. Bredeck (Fellow), St. Louis, Mo., is Health Commissioner of the City of St. Louis, having assumed his duties on April 20th last.

Dr. Delvan A. MacGregor (Fellow), Wheeling, W. Va., is now President of the West Virginia State Medical Association.

The West Virginia Heart Association was organized during May. The officers are Dr. Oscar B. Biern (Fellow), Huntington, President, Dr. George H. Barksdale (Associate), Charleston, Vice-President, and Dr. Raphael J. Condry (Associate), Elkins, Secretary.

Dr. Paul J. Connor (Fellow), Denver, Colo., has been elected President of the Colorado State Board of Health.

Dr William H Robey (Fellow), Boston, Mass, has been elected President of the Massachusetts Medical Society

Dr Jacob J Singer (Fellow), St Louis, Mo, Associate Professor of Clinical Medicine, Washington University School of Medicine, and Dr George H Hoxie (Fellow), Kansas City, Mo, President of the Missouri Tuberculosis Association have been named members of a committee to make a survey of tuberculosis control problems in Missouri

Dr B B Vincent Lyon (Fellow), Philadelphia, Pa, and Dr Russell S Boles (Fellow), Philadelphia, Pa, were elected first Vice-President and Secretary, respectively, of the American Gastro-Enterological Association at its last annual meeting

Dr John T King, Jr (Fellow), Baltimore, Md, was reelected Secretary of the Congress of Physicians and Surgeons of North America at the last meeting of that board

Dr John A McIntosh (Fellow), San Antonio, Texas, has been elected President of the Texas Neurological Society for the ensuing year

Dr John Zahorsky (Fellow), St Louis, Mo, has been appointed Director of the Department of Pediatrics of the St Louis University School of Medicine

Dr Mary M Spears (Fellow), Philadelphia, Pa, was recently elected the first woman member of the American Proctologic Society

Dr William deB MacNider (Fellow), Chapel Hill, N C, Professor of Pharmacology in the University of North Carolina Medical School, has been elected President of the American Society for Pharmacology and Experimental Therapeutics

Dr Alvin G Foord (Associate), Pasadena, Calif, has assumed the duties of President of the American Society of Clinical Pathologists Dr Frederick H Lamb (Associate), Davenport, Iowa, has been elected President-Elect

Dr LeRoy S Peters (Fellow), Albuquerque, N M, has been elected President of the American Sanatorium Association and a Director-at-Large for two years of the National Tuberculosis Association

OBITUARIES

DR WILLIAM HENRY MERCUR

Dr William Henry Mercur died at his home, in Pittsburgh, on July 16, 1933, at the age of seventy-two years Dr Mercur was born in Towanda, Pennsylvania, on January 19, 1861, the son of Mahlon Clark Mercur and Anna Hubbard Jewett Mercur After completing his preliminary education he entered the University of Pennsylvania School of Medicine from which he graduated in 1883 Later he pursued postgraduate studies in England, France, Germany and Switzerland, and then entered upon the practice of medicine in Pittsburgh

Dr Mercur was a member of the teaching staff of the Western Pennsylvania Hospital and College from 1883 to 1893, and of the Nurses Training School, Southside Hospital, from 1893 to 1910. He was a Founder and a Staff Member of the Pittsburgh Diagnostic Clinic from 1926 until his death.

He was a Fellow of the American College of Physicians from the time of its organization. He was a member of the Allegheny County Medical Society, the Pennsylvania State Medical Society, the American Medical Association, the American Climatological and Clinical Association, the American Therapeutic Society, the Association for Research in Nervous and Mental Disease and the American Association for the Advancement of Science. He was a member and, in 1901, President of the Pittsburgh Academy of Medicine.

Since 1911 Dr Mercur limited his practice to consultation work. He devoted much of his time and energy to social and public health problems. He early took an active part in widening the effectiveness of the city department of public health, and was responsible for instituting the use and availability of diphtheria antitoxin in the Pittsburgh district. He established and maintained at his own expense a library of medical and surgical reprints, probably the most complete in the country, which was freely available to any physician. His system of medical nomenclature and indexing of diseases is in use in many hospitals throughout the United States. He was deeply interested and largely instrumental in the organization and development of the Pittsburgh Diagnostic Clinic, the purpose of which is to render the highest type of medical service to persons of moderate means.

Dr Mercur, during his entire professional career, occupied an important niche in the medical and civil life of the community. He was a regular attendant upon medical meetings, deeply interested in all the problems of scientific medicine and of medical practice, and he will be greatly missed by a wide circle of friends.

E BOSWORTH MCCREADY, M D , F A C P

DR ROLAND E LOUCKS

Dr Roland E Loucks died of cardiac disease at his home, in Detroit, Michigan, on June 5, 1933. He had been in ill health for about two years but recently, after several months of confinement, he had recovered sufficiently to take care of his practice.

Dr Loucks was born at Smith Falls, Ontario, in 1869. After attending the schools of his native town he matriculated into the University of Maryland where he studied dentistry, obtaining the degree of D D S in 1893 when he was awarded the Gold Medal. He practiced dentistry for several years, after which he entered upon the study of medicine at Trinity University, Toronto, graduating in 1903. Dr Loucks located in Detroit where he practiced his profession for thirty years. About 1912, Dr Loucks be-

came interested in radiotherapy, directing his attention particularly to radium. He later used both radium and the x-rays. To qualify for his chosen specialty, he spent the year of 1914 in postgraduate study in London and Berlin. He became known and recognized both in the United States and Canada as a radiotherapist. He was one of the founders of the American Radium Society of which he was at one time president. He contributed extensively to the literature of his chosen specialty.

Dr. Loucks was a member of the American Roentgen-Ray and Radium Society, the Radiological Society of North America, a Fellow of the American College of Physicians, member of the Wayne County, Michigan State and American Medical Associations. He was radium therapist to Harper Hospital, Detroit, from 1916 to 1926. In 1926, he built and equipped the Memorial Hospital of which he was director until his death. During the years that Dr. Loucks confined his attention to a specialty he was a familiar figure at the annual meetings of the various national medical societies of which he was a member.

He is survived by his wife, one son and one daughter. He was a man not only of wide medical experience but of broad sympathies. He developed a sustaining philosophy of life that insured him a wide circle of intimate friends.

JAMES D. BRUCE, M.D., F.A.C.P.

DR. JUDD CAMPBELL SHELLITO

Dr. Judd Campbell Shellito (Fellow), Independence, Iowa, died in Cedar Rapids, April 16, 1933, of injuries sustained in an automobile collision that day. His death was due to a basal skull fracture, with probable internal injuries. An occupant of the other car in the collision was also killed. Dr. Shellito was returning from Council Bluffs, where he had attended the spring meeting of the Iowa Clinical Medical Society, of which he was Secretary-Treasurer.

Dr. Shellito was born in Independence, Iowa, May 25, 1889. He attended high school at Pasadena, Calif., and at Evanston, Ill. He graduated from Princeton University in 1911, and from Johns Hopkins University School of Medicine in 1915. His internship was served at the Harper Hospital, Detroit. In 1917, he enlisted in the U. S. Army Medical Corps, and was stationed for some time at the Cook County Hospital, Chicago, and later at Fort Riley, Kansas. He served with the American Expeditionary Forces in France for a year and a half, having charge of the X-Ray Department of Hospital No. 3 in Paris. After the war, he returned to Independence, and became associated in the partnership of Drs. Shellito and Agnew.

He was a member of the Buchanan County Medical Society, the Iowa State Medical Society, the Iowa Clinical Society, the Austin Flint Cedar Valley Medical Society, the Iowa X-Ray Club, the Radiological Society of

North America, a Fellow of the American Medical Association and a Fellow of the American College of Physicians since 1931

He was also active in civic affairs, being a past President of the Rotary Club, on the local Boy Scout court of honor, and a Trustee of the First Methodist-Episcopal Church. He was long active in the management of the People's Hospital, being a member of its Board of Directors and of its Executive Committee

"Dr Shellito was an outstanding factor in his community, a man of action in varied fields, professional, religious, social and civic. In his activities for his church, in the medical societies with which he was affiliated, and in his membership of other organizations, he gave of his best, devoting time, finances and of his talents to bring to success any undertaking he assumed. He had the courage of his convictions, he was, perhaps, blunt in speech, but always open and aboveboard, without subterfuge, always working for the best as he saw it. A man of innate honesty of purpose and ability, he was an asset to the community and in any movement in which he had a part."

ELMER G. SENTY, M D , F A C P

DR THOMAS WRAY GRAYSON

Dr Thomas Wray Grayson (Fellow) died May 17, 1933, at his home in Pittsburgh, of cerebral hemorrhage. Dr Grayson was born November 22, 1871, at Meadville, Pennsylvania. He attended the Meadville and Washington High Schools and received his B A and M A degrees from Washington and Jefferson College. In 1897 he graduated from the Western University of Pennsylvania Medical School, served his internship at the West Penn Hospital and after postgraduate courses in New York and Berlin, began the practice of medicine in Pittsburgh, specializing in internal medicine. His death removes from the profession and the community an active and valuable member. Deeply interested in civic affairs, Dr Grayson took a prominent part in the activities of the Civic Club of Pittsburgh and acted as Chairman of several committees which were largely instrumental in the installation of medical inspection and open-air classes in the public schools. A devout churchman, he was a communicant of the Church of the Ascension and a trustee of the Episcopal Diocese of Pittsburgh.

He was a member of the American Legion, the Officers Reserve Corps, the Military Order of the World War, and belonged to the University and Sojourners Clubs and the Phi Gamma Delta Fraternity. He was elected to Fellowship in the American College of Physicians in 1920. He was a member of his county and state societies and of the American Medical Association. He was also a member, and one time treasurer, of the American Gastro-enterological Society. At the time of his death he was on the staffs of the Presbyterian Hospital and the Protestant Home for Incurables.

E. BOSWORTH MCCREARY, M D , F A C P

NATIONAL DIPHTHERIA TOXOID



Toxoid is stable, gives protection in from 90 to 95 per cent of patients that may last for life. Reactions are practically absent, particularly in young children. Toxoid retains its potency for two years or longer and contains no alien serum. It cannot sensitize patients to the proteins contained in any antitoxin that may be indicated in later life. Every effort should be exerted to wipe out diphtheria by immunization with Toxoid. We furnish, without charge, leaflets on diphtheria immunization to physicians for enclosing in their bills, statements, or for distribution by health and school authorities, without advertisement or firm mentioned. Send for as many of these leaflets as you will use.

NATIONAL SMALL POX VACCINE



Prevents Small Pox!

Vaccinate Now!!

National Small Pox Vaccine is subjected to careful bacteriologic and clinical tests to ensure a potent product, giving a high percentage of "takes," and is free from pathogenic organisms.

Five tubes of Vaccine and a package of Toxoid sent for \$1 00. Use coupon.

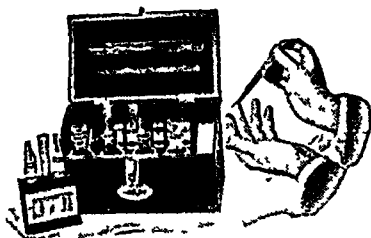
THE NATIONAL DRUG COMPANY
PHILADELPHIA
U.S.A.

Enclosed find \$1 00 for five tubes Small Pox Vaccine and package of Toxoid and _____ Toxoid Leaflets per adv in Annals of Internal Medicine

Name _____ Date _____

Address _____

LaMOTTE Blood Sugar Outfit



For rapid estimation of blood sugar in determining sugar tolerance of diabetic patient
Uses only few drops of finger blood

Permits tests at close intervals
Invaluable for infant cases
Accurate to 10 mg of sugar per 100 c c of blood
Direct result without calculations
Only 20 minutes required for complete test
Complete with instructions, price \$24 00,
f o b Baltimore, Maryland

Your LaMotte Blood Chemistry Handbook* illustrates and describes many other simple, accurate testing outfits developed by LaMotte Research Department in cooperation with recognized specialists

* If you do not have one, write today for a complimentary copy

LaMOTTE Chemical Products Co.

418 Light Street

Baltimore, Md

CURDOLAC FOODS LENGTHEN DIABETIC LIVES

Blood sugar producing properties are low because these foods are

- 1 Moderate in carbohydrate content, yet
- 2 Not excessive in protein and fat.

(58% of the protein and 10% of the fat consumed produce sugar in the blood.)

Samples and literature on request

CURDOLAC FOOD CO.
Box 299 Waukesha, Wis.

Reader! Subscriber!



The advertisements in this journal are approved by a special Advertising Committee of the American College of Physicians. Advertisements of pharmaceutical products are also approved by the Council on Pharmacy and Chemistry.

These advertisements are dignified, well planned and attractively printed.

These advertisers merit the confidence and support of our subscribers everywhere.

Advertisers want to know that you read their advertisements in this journal, and they are anxious to check the source of inquiries and orders. You will perform a real service, both to the journal and to the advertiser, if you will mention ANNALS OF INTERNAL MEDICINE whenever ordering or sending inquiries concerning products herein advertised.

THE DESERT SANATORIUM OF TUCSON, ARIZONA

ALLEN K. KRAUSE, M.D., *Director*

W. PAUL HOLBROOK, M.D.
Physician-in-Chief

CHARLES W. MILLS, M.D.
Chief, Visiting Staff

MAX PINNER, M.D.
In Charge, Laboratories & Research

¶Offers the facilities and services of its splendidly and completely equipped Out-patient Department for the diagnosis and treatment of acute and chronic disease during the summer

¶Caring for both ambulant patients and those confined to bed in quarters outside the Sanatorium

¶Hot, dry, desert climate especially beneficial for chronic sinusitis, pulmonary affections of various types, hypertension, arthritis, etc

¶Special Department of Physiotherapy Heliotherapy, when indicated, administered under proper safeguards

Accommodations obtainable in Tucson and neighborhood

For information and rates, address Miss B. M. Dickey, Administrative Secretary

1933 DIRECTORY *of the* AMERICAN COLLEGE OF PHYSICIANS

A new Directory of the Masters, Fellows and Associates of the American College of Physicians, containing complete alphabetical and geographical rosters, has been published and recently distributed to every member in good standing. Members will kindly communicate with the Executive Secretary of the College concerning non-receipt of copies, revision for the next issue, and other relevant matters.

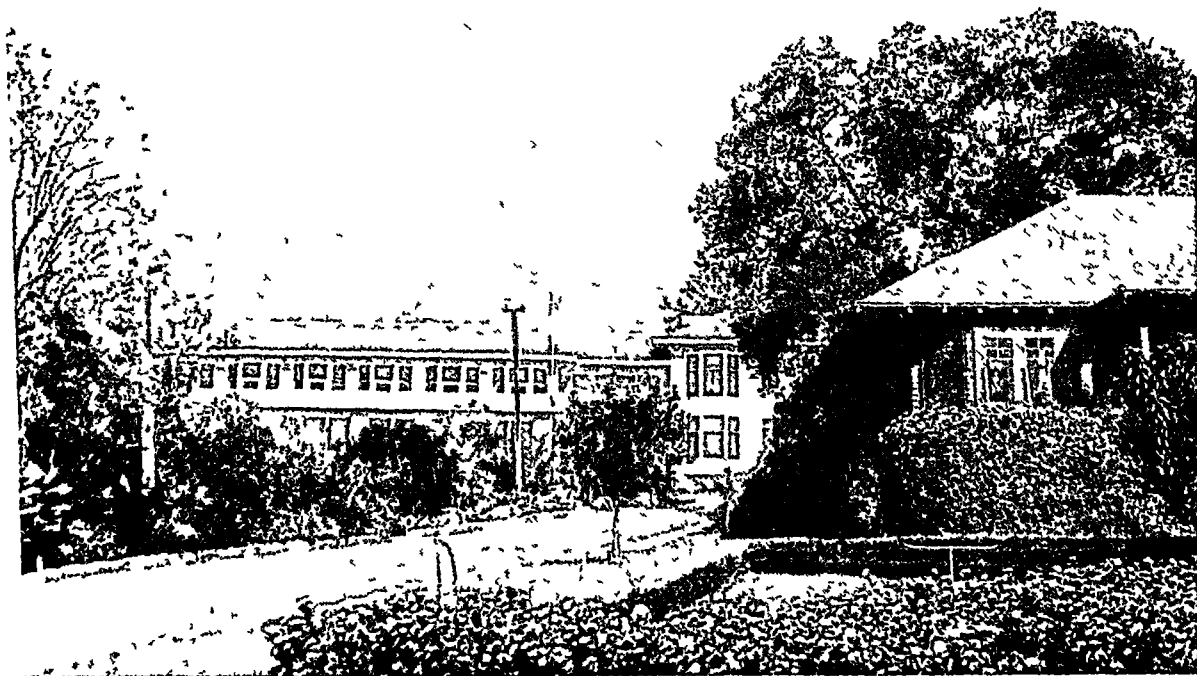
The WYATT CLINIC *for* Chronic Arthritis



TUCSON, ARIZONA

THE POTTENGER SANATORIUM AND CLINIC FOR DISEASES OF THE CHEST

Monrovia, California



THIRTY YEARS' EXPERIENCE IN THE TREATMENT OF TUBERCULOSIS

LOCATION

Sixteen miles east of Los Angeles In the foothills of the Sierra Madre Mountains, at an elevation of 1000 feet On the main line of Santa Fe Railway Connected with Los Angeles by interurban railway and splendid boulevards

ENVIRONS

The grounds consist of a beautiful park of forty acres, in which are found a variety of native Live Oaks, subtropical trees and plants, and a profusion of beautiful shrubs and flowers Many winding walks and nooks of exquisite beauty add to its attractiveness When on exercise, patients also enjoy the beautiful trails in the adjoining canyons and mountains

MEDICAL CARE

Competent resident staff Examinations for comparison every six weeks Patients visited twice daily Their individual needs and problems receive close personal attention

THERAPEUTIC CARE

Fads are not followed, but an endeavor is made to give patients the amount of rest and exercise suited to their individual needs, the benefits of a liberal and adequate diet, such tonic measures as will increase their resistance, and other measures that will help them overcome any disturbing symptoms or complications that may arise Heliotherapy, tuberculin, pneumothorax and surgery employed whenever indicated

DIAGNOSTIC CLINIC

A diagnostic clinic is maintained for the study of all diseases of the chest
Weekly rates from \$30 up, including medical attention, medicines (except expensive remedies) and general nursing Extra charge for operative measures (except pneumothorax)

F. M. POTTENGER, M D, Medical Director

For Particulars Address

THE POTTENGER SANATORIUM, Monrovia, California

THE ANALYSIS SHOWS

THE VALUABLE ALKALINE CHARACTER OF

VICHY CÉLESTINS

Natural Mineral Water

INDICATIONS

In stomach and
liver affections
and digestive disorders
in general;
in gout, arthritis
associated with uric
acidemia, uricemia,
and nephrolithiasis of
uric acid origin.



BOTTLED
AT THE SPRING
VICHY, FRANCE

ANALYSIS (GRAMS PER LITER)

Sodium bicarbonate	3 3090
Potassium bicarbonate	0 2490
Lithium bicarbonate	0 0281
Calcium bicarbonate	0 7400
Magnesium bicarbonate	0 1016
Ferrous bicarbonate	0 0012
Sodium chloride	0 3830
Sodium sulphate	0 2430
Silica	0 0300
Sodium arsenate, Phosphate and nitrate	} present

Brochure with Therapeutic Data and Medical Bibliography
sent on request.

Sole United States Agents, American Agency of French Vichy, Inc., 503 Fifth Ave, New York

THE DESERT SANATORIUM OF TUCSON, ARIZONA

ALLEN K. KRAUSE, M.D., *Director*

W. PAUL HOLBROOK, M.D.
Physician-in-Chief

CHARLES W. MILLS, M.D.
Chief, Visiting Staff

MAX PINNER, M.D.
In Charge, Laboratories & Research

¶Offers the facilities and services of its splendidly and completely equipped Out-patient Department for the diagnosis and treatment of acute and chronic disease.

¶Caring for both ambulant patients and those confined to bed in quarters outside the Sanatorium.

¶Hot, dry, desert climate especially beneficial for chronic sinusitis, pulmonary affections of various types, hypertension, arthritis, etc.

¶Special Department of Physiotherapy. Heliotherapy, when indicated, administered under proper safeguards.

Accommodations obtainable in Tucson and neighborhood

For information and rates, address Miss B. M. Dickey, Administrative Secretary

Consultation and Advisory Service

ON

HOSPITAL PLANNING

ORGANIZATION

MANAGEMENT

AND EQUIPMENT

•

SURVEYS CONDUCTED FOR
INDIVIDUAL HOSPITALS OR
ENTIRE COMMUNITIES

•

Office of

WILLIAM HENRY WALSH, M.D.
612 North Michigan Avenue
CHICAGO

The WYATT CLINIC

for

Chronic Arthritis

•

TUCSON, ARIZONA

BOOKS

FOR THE PHYSICIAN'S LIBRARY

Adler's CLINICAL PHYSIOLOGY OF THE EYE	\$5 00	Horgan's RECONSTRUCTION OF THE BILIARY TRACT	\$4 00
Anderson's DETACHMENT OF THE RETINA	\$4 50	Humphris' PHYSIOTHERAPY	\$4 50
Barclay's THE DIGESTIVE TRACT	\$12 00	Huxley's ELEMENTS OF EXPERIMENTAL EMBRYOL- OGY	Preparing
Baur-Fisher-Lenz' HUMAN HEREDITY	\$8 00	James' HISTORY OF OPHTHALMOLOGY IN ENGLAND	\$4 00
Bloomfield-Polland's GASTRIC ACIDITY	\$2 50	Knox' X-RAY THERAPEUTICS	\$7 00
Cameron's TEXTBOOK OF BIOCHEMISTRY, 4th ed	\$3 75	Landman's HUMAN STERILIZATION	\$4 00
Capps' PAIN IN THE PLEURA, PERICARDIUM AND PERITONEUM	\$3 00	Lewis' DISEASES OF THE HEART	\$3 50
Clifford's THE SPUTUM	\$4 00	Needham's CHEMICAL EMBRYOLOGY	\$26 50
Cowdry's ARTERIOSCLEROSIS	\$5 00	Osgood-Allison's FUNDAMENTALS OF ORTHOPAEDIC SURGERY	\$3 00
Dawson's HISTORY OF MEDICINE	\$2 50	Parson's DISEASES OF THE EYE	\$4 50
Dixon's THE MANO-METRIC METHODS FOR MEAS- URING CELL RESPIRATION	Preparing	Rackemann's CLINICAL ALLERGY	\$7 50
Doll-Phelps-Melcher's MENTAL DEFICIENCY DUE TO BIRTH IN- JURIES	\$4 50	Rasmussen's PRINCIPAL NERVOUS PATHWAYS	\$2 50
Emerson's ALCOHOL AND MAN	\$4 50	Rockwell's STREPTOCOCCIC BLOOD STREAM INFECTIONS	\$1 75
Fisher's INTERNAL DERANGEMENTS OF THE KNEE- JOINT	\$3 50	Stern's CLINICAL DIAGNOSIS PHYSICAL AND DIF- FERENTIAL	\$3 50
Friedenwald's PATHOLOGY OF THE EYE	\$3 50	Stryker's COURTS AND DOCTORS	\$2 00
Harrison's CHEMICAL METHODS IN CLINICAL MEDI- CINE	\$5 25	White's HEART DISEASE	\$7 50
Holmes' CANCER AND SCIENTIFIC RESEARCH	\$1 50	Wilson's FRACTURES AND COMPOUND FRACTURES	\$10 50
		Zinsser's RESISTANCE TO INFECTIOUS DISEASES	\$5 00

THE MACMILLAN COMPANY

60 FIFTH AVENUE

PUBLISHERS

NEW YORK

Bromural

Alphabromisovalerylcarbamide

Council Accepted

AS A ROUTINE SEDATIVE

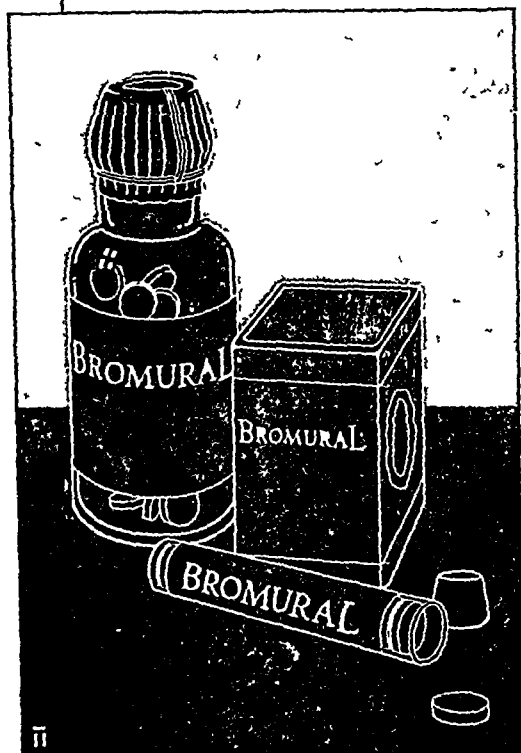
in general nervous disturbances prescribe one tablet (5 grains) several times a day. As a mild and prompt hypnotic the dose is 2 to 3 tablets upon retiring or during the night. Bromural is not a barbiturate nor a bromide.

5 grain tablets and as a powder.

Samples and literature upon request

Bilhuber-Knoll Corp.,

154 Ogden Avenue, JERSEY CITY, N. J.



Exclusively Engaged
in providing

Professional Protection

Thirty-Four Years



The Medical Protective Company
of Fort Wayne, Ind.

WHEATON

:

:

:

:

ILLINOIS

Please Mention this Journal when writing to Advertisers

Devitt's Camp, Inc.

ALLENWOOD
PENNSYLVANIA

(Tuberculosis)

*On beautiful White Deer Mountain, 20 miles southeast
of Williamsport, Pa.*

All modern methods of treatment, including heliotherapy, artificial pneumothorax, phrenic exaeresis, Jacobaeus operation, and thoracoplasty

Not operated for profit Moderate rates Modern buildings

Patients given individual attention by experienced physicians and specially trained registered nurses

The following physicians will be glad to examine patients for admittance to Camp

J M ANDERS, M D, Philadelphia, Pa
ISABEL M BALPH, M D, Philadelphia, Pa
E J G BEARDSLEY, M D, Philadelphia, Pa
WARD BRINTON, M D, Philadelphia, Pa
F W J BURGE, M D, Philadelphia, Pa
DAVID A COOPER, M D, Philadelphia, Pa
DONALD R FERGUSON, M D, Philadelphia, Pa

JOHN B FLICK, M D, Philadelphia, Pa
JOHN A KOLNER, M D, Philadelphia, Pa
W ESTELL LEE, M D, Philadelphia, Pa
A C MORGAN, M D, Philadelphia, Pa
ARTHUR W PHILLIPS, M D, Philadelphia, Pa

GEO MORRIS PIERSOL, M D, Philadelphia, Pa

EDWARD R SNADER, Jr, M D, Philadelphia, Pa

MERVYN R TAYLOR, M D, Philadelphia, Pa
THOS J VISCHER, M D, Philadelphia, Pa
A S KECH, M D, Altoona, Pa

CHARLES C HABLSTON, M D, Baltimore, Md

CHARLES S AITKEN, M D, Brookline, Pa
J C ATWELL, M D, Butler, Pa
F DECARIO, M D, Bradford, Pa
J W WOOD, M D, Chester, Pa

JOHN E FRETZ, M D, Easton, Pa
RICHARD R DALRYMPLE, M D, Erie, Pa
JESSE L LENKER, M D, Harrisburg, Pa
H B ANDERSON, M D, Johnstown, Pa
JOHN H ESBENSHADE, M D, Lancaster, Pa
E J WERLE, M D, Meadville, Pa
CHARLES G CRANE, M D, Newark, N J
W A WOMER, M D, New Castle, Pa
EDWARD S MCSWEENEY, M D, New York City

M THERESA SCANLAN, M D, New York City

STANLEY L WANG, M D, New York City
W R GLENNEY, M D, Pottsville, Pa

R R JONES, M D, Pittsburgh, Pa

C L PALMER, M D, Pittsburgh, Pa

A H COLWELL, M D, Pittsburgh, Pa

HOWARD U MILLER, M D, Reading, Pa

A E DAVIS, M D, Scranton, Pa

H D WILLIAMS, M D, Trenton, N J

B M ALLEN, M D, Wilmington, Del

JOHN MINOR, M D, Washington, D C

J W PEABODY, M D, Washington, D C

H R SCHREIBER, M D, Washington, D C

E W BIABY, M D, Wilkes Barre, Pa

HARRY M READ, M D, York, Pa

BOOKLET

ROSS K CHILDERHOSE, M D

JOHN S PACKARD, M D

Associate Physicians

WILLIAM DEVITT, M D

*Superintendent and
Physician in Charge*

In Erysipelas Use Antitoxin

Erysipelas Streptococcus Antitoxin marks a distinct advance in the specific treatment of erysipelas. Prior to its development, the course of the disease was uninfluenced by the application of local remedies. With its advent, there was frequently noticed a prompt improvement in the toxic depression and critical drop in temperature and pulse rate within 18 hours, rapid cessation in the spread of the local lesion with hastened regression of swelling, and conspicuous shortening of the hospitalization. Continued clinical trial has confirmed its efficacy—notably the huge series of 3311 cases at Bellevue Hospital, which demonstrates a 30% mortality reduction and a 60% reduction in the duration of the disease. These figures afford ample reason for giving Erysipelas Streptococcus Antitoxin Lederle to every erysipelas patient.

Erysipelas Streptococcus Antitoxin-Lederle (refined and concentrated) is supplied in packages of one therapeutic dose of approximately ten cubic centimeters.

Literature sent on request



LEDERLE LABORATORIES, INC.
511 Fifth Avenue, New York

Eliminating Doubt from the Electrocardiographic Record



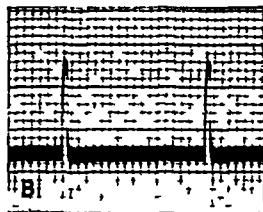
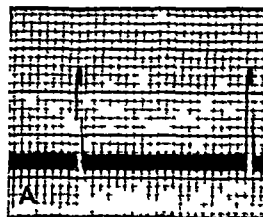
Importance of high and constant speed of deflection

AS explained by a well-known authority, the initial changes in the potentials to be recorded from the heart are rapid, and if the quickest movement of which the galvanometer is capable is too slow to follow these changes, accuracy is lost, distortion occurs when the natural frequency of the galvanometer is below that of the oscillations recorded.

In this respect, the Victor Electrocardiograph, due to the principle of tube amplification, precludes any possibility of obtaining an inaccurate record. Regardless of the amount of body resistance, the operator ignores it entirely, for it cannot affect the high speed of deflection that characterizes the Victor instrument. As the galvanometer is permanently set at the factory and sealed in oil, this high speed of deflection is constant under all conditions of operation. There is no string to adjust, no change in operating procedure, no variable to cast doubt as to the accuracy of the record.

Two previous advertisements (copies on request) have explained how the annoying factor of overshooting has been eliminated and

why compensation for skin current is unnecessary with the Victor Electrocardiograph. These are distinct advantages in that they contribute to simplicity of operation, consistent performance and reliable records.



DEMONSTRATION

Proving that high resistance has no effect on speed of deflection with the Victor (amplifying type) Electrocardiograph

(A) 10 mm deflection per 1 millivolt input—no external resistance. Note speed of deflection.

(B) Same set up of instrument, but with 10,000 ohms non inductive resistance added to external circuit. Note that there is no change in the speed of deflection.

Write for complete information on the new model Victor Electrocardiograph, incorporating a timing device and automatic lead markers, and with which either film or paper may be used.

GENERAL ELECTRIC  **X-RAY CORPORATION**

2012 Jackson Blvd.

Formerly Victor X-Ray Corporation

Chicago, Illinois



the
cardiologist
is assured
of dependability
in
digitalis
administration

EACH PILL CONTAINS
0.1 GRAM (1½ GRAINS)
OF DIGITALIS.
PHYSIOLOGICALLY
STANDARDIZED

Send for sample and literature

DAVIES, ROSE & CO., Ltd.
Pharmaceutical Manufacturers
BOSTON, MASS.

CURDOLAC FOODS LENGTHEN DIABETIC LIVES

Blood sugar producing properties
are low because these foods are.

1. Moderate in carbohydrate content, yet
2. Not excessive in protein and fat

(58% of the protein and 10% of the fat consumed produce sugar in the blood)

Samples and literature on request

CURDOLAC FOOD CO.
Box 299 Waukesha, Wis.

LAMOTTE SERVICE

IMPROVED KLINE ANTIGEN FOR PRECIPITATION TESTS FOR SYPHILIS

This improved Antigen is now being produced under an exclusive arrangement with the Mount Sinai Hospital of Cleveland, in whose laboratory the method of preparation was developed. Each lot of antigen is tested in this same laboratory and only approved Standard Antigen is released by us for distribution.

Far superior in the sero diagnosis of syphilis.

May be used for tests on spinal fluid. Antigen solution has excellent keeping qualities.

Sensitive at low temperatures.

Prices and full information on the antigen and the new simplified compact outfits for these tests sent on request.

Your LaMotte Blood Chemistry Handbook * illustrates and describes many simple accurate testing outfits developed by LaMotte Research Department in cooperation with recognized specialists.

* If you do not have one, write today for a complimentary copy.

LAMOTTE CHEMICAL PRODUCTS CO.
418 Light St. Baltimore, Md



Leaving Nothing to Chance

Digitalis is such a potent drug and digitalization such a delicate procedure that a grave responsibility rests on the shoulders of the pharmaceutical manufacturer. Appreciating this very fully, John Wyeth & Brother exercise every known precaution to safeguard the various stages of production, assay, potency of

WYETH'S CAPSULES DIGITALIS LEAF (DEFATTED)

Because of obvious variation associated with biological assay, Wyeth insist on a double check system of standardization.

Each batch is carefully assayed by both the U S P. frog method and the cat method of Hatcher and Brody. Only those batches showing concordant results are accepted.



Dosage accuracy is assured by supplying Wyeth's Digitalis in capsules—each capsule containing the equivalent of 15 minims of U S P tincture of Digitalis (one cat unit).

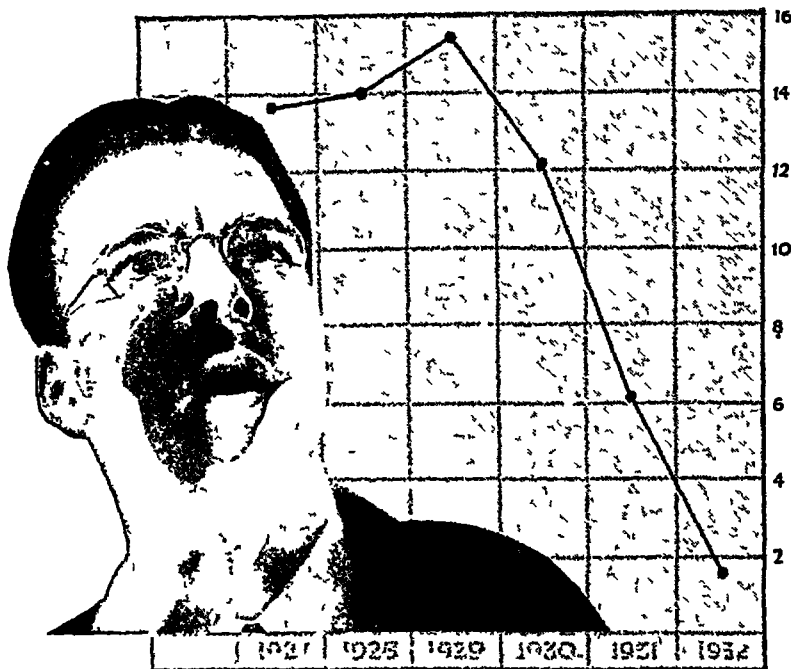
In this way the disadvantages of the drop method of measuring dosage are completely obviated—a vital safeguard particularly in the case of the ambulant patient.

Control the integrity of your prescriptions
by specifying Wyeth's pharmaceuticals.

JOHN WYETH
PHILADELPHIA, PA



& BROTHER, INC.
WALKERVILLE, ONT



Diphtheria Death Rate per 100 000 of Population in the City of Chicago

SHOUTING *down the* DEATH RATE

OTHER cities have made notable reductions in the incidence of diphtheria and in the mortality rate from the disease—but Chicago's record is spectacular

In 1930 the diphtheria mortality rate was 12.1 per hundred thousand population. In October, 1930, the campaign began. Bulletins were sent to mothers, and letters to physicians. Four hundred nurses made over half a million calls—teachers told their pupils—pastors their congregations—radio talks reached the masses. The result was inevitable. The immunization rate went up and the mortality rate came down. And

when 1932 came to a close over 300,000 children were immunized. They had virtually shouted down the diphtheria death rate to 1.9 per hundred thousand.

Modern methods of diphtheria control available to every community have brought new low records in diphtheria incidence and mortality. The House of Squibb is pleased to have played a part. It provides efficient service to Boards of Health and individual physicians. It has available a complete line of Diphtheria Products—the finest that long experience and painstaking care can produce.

DIPHTHERIA ANTITOXIN SQUIBB—For temporary prophylaxis and for treatment

DIPHTHERIA TOXIN-ANTITOXIN MIXTURE SQUIBB—For active immunization of individuals susceptible to diphtheria. Prepared with concentrated diphtheria antitoxin from sheep.

DIPHTHERIA TOXOID SQUIBB (Anatoxin Ramon)—For active immunization against diphtheria.

DIPHTHERIA TOXIN SQUIBB FOR SCHICK TEST—Diluted, ready for use. To determine susceptibility to diphtheria.

LITERATURE giving complete information regarding Squibb Diphtheria Products will be sent upon request—address Professional Service Department, E. R. Squibb & Sons, 745 Fifth Avenue, New York City.

E. R. SQUIBB & SONS, NEW YORK
MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858.

MALTINE

With Cod Liver Oil

IS WELL TOLERATED

IT IS a matter of considerable concern to physicians that plain cod liver oil is not well tolerated, particularly by infants, when administered in successive doses.

Clinical tests have shown that Maltine With Cod Liver Oil is better tolerated and more easily assimilated than plain cod liver oil by both infants and adults

Seventy per cent of this preparation is Maltine, a concentrated extract of the nourishing elements of malted barley, wheat and oats—rich sources of Vitamin B (b₁) and

containing Vitamin G (b₂) The balance is pure, vitamin-tested cod liver oil Maltine With Cod Liver Oil has a Vitamin A potency of at least 450 U S P. units per gram Its Vitamin D potency is such that rachitic rats, fed 10 mg daily, showed perceptible to distinct healing of rickets in from 6 to 10 days by the line-test method

When taken with orange or tomato juice in adequate dosage, Vitamin C is added to the guaranteed Vitamin A, B (b₁), D and G (b₂) content of MALTINE With Cod Liver Oil The preparation is palatable, nutritious, well tolerated and readily digested—even by infants Biological report on request The Maltine Company, 30 Vesey Street, New York Est 1875.



THE ORIGINAL

Maltine

WITH COD LIVER OIL

Introduced in 1875

MEAD'S 10 D COD LIVER OIL WITH VIOSTEROL

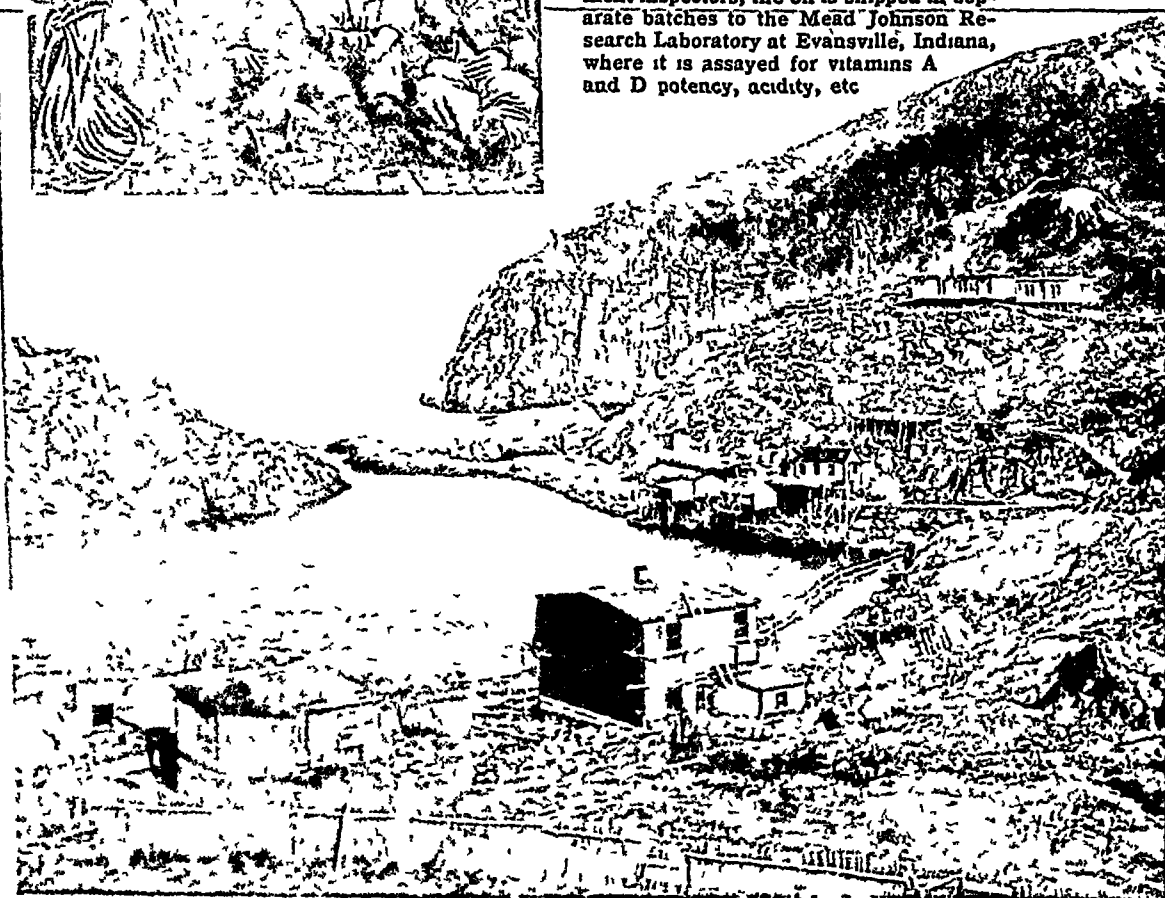
is made from ergosterol prepared in our own laboratory from yeast cultured according to our own specification, activated by our own designed lamps and our own technic of activation, and added to Mead's Newfoundland Cod Liver Oil, and is the vehicle of choice (for vitamins A and D prophylaxis) of a large number of physicians who feel bewildered by the increasing

number of vitamins A-D products on the market. For curative purposes, and for prophylaxis in severe rickets, their preference is Mead's Viosterol in Oil 250 D or Mead's Viosterol in Halibut Liver Oil 250 D. Mead Johnson and Company, Evansville, Indiana, U.S.A., Pioneers in Vitamin Research, Send for free Comparative Dosage Chart.



(1) TYPICAL NEWFOUNDLAND COD FISHERMEN

They catch the fish in traps and quickly land their catch alive at the Mead Johnson rendering stations. The rendering process is quickly done at these stations, under supervision of the Newfoundland Government inspectors, the oil is shipped in separate batches to the Mead Johnson Research Laboratory at Evansville, Indiana, where it is assayed for vitamins A and D potency, acidity, etc.



(2) A BIT OF RUGGED NEWFOUNDLAND SCENERY

near the harbor of St. John's, the center of the cod fishing industry. The cod liver oil used by Mead Johnson & Co. is of origin exclusively at Newfoundland. Professors Drummond and Hilditch, in their tests of natural, unadulterated oils from the livers of cod fish have found Newfoundland Cod Liver Oil superior in Vitamins A and D content to cod liver oils from Iceland, Scotland and Norway.

For information regarding the use of Mead Johnson products to cooperate in preventing rickets, please write to the author or persons

ANNALS OF INTERNAL MEDICINE

VOLUME 7

OCTOBER, 1933

NUMBER 4

COLLAPSE THERAPY OF BRONCHIECTASIS *

By E RIST, M D , *Paris, France*

It was to be expected that artificial pneumothorax, having proved so strikingly efficient in healing ulcerative tuberculosis of the lungs, should also be attempted as a therapeutic measure against bronchiectasis. Indeed the attempt was made for the first time as early as 1903 by one of Forlanini's most brilliant followers, Riva-Rocci, and it was, we hear, crowned with success. Since then several authors have published cases of bronchiectasis treated by pneumothorax, with a variety of results, but the sum of those cases amounts to a comparatively small total. Whittemore and Balboni could in 1928 gather only 93 of them out of the world literature. It seems, therefore, as if each series consisted of only a few cases, none of the authors having been persevering enough to give the method a systematic trial. As a matter of fact, this method of therapy has not become widespread, and one still meets with skepticism or reluctance on the part of the practitioner, when proposing to collapse by pneumothorax a lung affected with bronchiectasis. Yet there has been lately the reverse from indifference regarding the disease itself, to wit the remarkable improvements which radiography after injecting the bronchial tree with iodized oil, to say nothing of bronchoscopy, have achieved in its diagnosis.

I think some misconceptions have been at work to prevent physicians from taking advantage as often as they should of the resources which artificial pneumothorax puts at their disposal against bronchiectasis. In the first place, they are not sufficiently aware that there is no such thing as spontaneous recovery from that malady. One still reads in some textbooks and articles that recovery may occur and consequently justify expectancy. But, to my knowledge, no valid instance has ever been produced. In the second place one is too apt to forget that it is not only an incurable, but, in the long run, a deadly disease. It is true that it may for some time—months or even years—remain a comparatively harmless ailment, as long as the supuration is due to the ordinary aerobic micrococci. Sooner or later, however, a time inevitably comes when the bronchiectatic focus is invaded by

* Read at the Montreal Meeting of the American College of Physicians, February 8, 1933

anaerobic bacteria and eventually by the spirochetes, which give the infection its peculiarly serious septic character. The change is signaled by the offensive nature of the discharge, which was previously odorless.

Once this stage has been reached, the patient, although his general condition may at first remain tolerably good, is threatened by all the dangers which attend anaerobic infection of the lung. Multiple small abscesses develop in the neighborhood of the cylindrical bronchiectases and add to the lipiodol roentgen-ray picture the characteristic pigeon-hole or grape-bunch features. Various circumstances favor acute revivals of the infectious process, which may extend to further parts of the lung, either in the immediate vicinity of the primary focus, or by way of embolism, to more distant parts of the same or to the opposite lung. Real gangrene of the lung is liable to occur in such circumstances. If the process extends to the visceral pleura and there are no adhesions, a putrid, offensive empyema is not seldom observed. Sometimes a more or less evident pyemia occurs with septic emboli which have a curious propensity to localize either in the medulla of the long bones or in the substance of the brain. The metastatic abscesses thus produced are always characterized by their foul, offensive odor. I should mention also the very profuse recurrent hemorrhages which complicate some cases.

Even if the patient does not succumb to one or several of the aforementioned accidents, he is sure to reach a period when progressive wasting, cachexia and eventually amyloid will put an end to his life. It matters little whether the whole story runs along for three or 10 or 25 years. Bronchiectasis is a disease which finally kills, be the end as protracted as we may pray for. Therefore, if one keeps this in mind, one must feel that it should be treated as early and as effectively as possible.

There is another misconception which has prevented many a physician from attempting pneumothorax, namely the notion that bronchiectasis is almost always accompanied by symphyseal pleural adhesions rendering a trial perfectly useless. Now I think it is always unwise to predict confidently the presence (or the absence) of adhesions, even when the history of the patient and his physical and roentgen-ray examination seem to overwhelm us with evidence, because the only definite evidence is the failure of our attempts to create a pneumothorax. As a matter of fact, there is very little truth in the widespread notion that adhesions are almost the rule in bronchiectasis. Among the 93 cases collected from the literature by Whittemore and Balboni, 12 only had adhesions which made a collapse impossible. Of course, the 93 cases being, as I have said before, the sum of numerous isolated cases or small series of cases published by a number of authors, one may presume that many a failure caused by adhesions has escaped publication. The percentage of 12.9 resulting from these figures is evidently much too low. In the rather large series of personal cases which I shall presently discuss, I find 37.2 per cent of failures attributable to adhesions, a little more than one-third. Tabulating in 1926 more than a thousand per-

sonal cases of tuberculosis treated by pneumothorax, I found the number of failures due to extensive adhesions to be one-fourth of the total. Even admitting, therefore, that adhesions are somewhat more frequent in bronchiectasis than in tuberculosis, still certainly the difference is not such as would justify abstention by principle from pneumothorax in bronchiectasis, while there is now a consensus of opinion that pneumothorax is, or ought to be, the routine treatment of ulcerative tuberculosis.

Furthermore, I feel certain that the proportion of pleural adhesions is greater in cases of long standing than in recent cases. There is therefore good reason to believe that if we treated bronchiectasis earlier and more systematically with pneumothorax the proportion of failures caused by adhesions would be less. And finally if we fail to collapse the lung by pneumothorax, we may try to collapse it by phrenicectomy.

I now wish to present a short account of the cases of bronchiectasis which have been observed in my Hospital-Department during a period running from 1920 up to the end of 1931. Their total number is 90, of which 31 were not submitted to artificial pneumothorax, either because they refused treatment and were ultimately lost sight of, or because they were admitted in an extremely serious condition, precluding any sort of active therapeutic measure. As a matter of fact, the five patients belonging to this last group died in the wards soon after admission, one with abscess of the lung, two with lung gangrene, and two with septic bronchopneumonia.

In 59 cases, artificial pneumothorax was attempted. We failed to create it in 22 cases, the pleura being totally or extensively adherent. Among the 37 patients whose lung could be successfully collapsed 17 were not benefited by it. Six of these 17 had adhesions of the diaphragmatic pleura, therefore, although the rest of the lung was well collapsed, its inferior part, where the lesions were located, remained uninfluenced. In one other patient the lung was beautifully collapsed, in fact he was one of the most remarkable instances of perfect collapse which I have ever witnessed; the lung was reduced to the size of a fist around the hilus. But we soon noticed that each refill of the pleural cavity with air stopped the discharge entirely and was followed by high fever. If we let the lung expand again to a certain degree, an abundant foul discharge of pus began to flow and the fever subsided. The roentgen-ray picture showed, in the center of the collapsed lung, a small, walnut-sized, round cavity half filled with fluid. Evidently the collapse produced a kink of the evacuating bronchus and consequently a retention of the purulent discharge. We tried in vain to approximate a medium pressure which would facilitate drainage and exclude retention, and the treatment had to be abandoned. The remaining 10 unsuccessful pneumothorax cases were either cases of bilateral bronchiectasis or were complicated with gangrene of the lung and ultimately died.

There remains a group of 20 patients, one-third of the total, who derived the greatest possible benefit from pneumothorax treatment. They were rapidly made free of all morbid symptoms, their discharge rapidly disap-

peared, they ceased coughing, running fever and losing weight, they were to all appearances restored to health. It is true that for seven of them the recovery was conditional to the maintenance of lung collapse. If we allowed the lung to expand, the symptoms, after a certain time, would appear again, to vanish once more as soon as the pleural cavity was refilled with air. Even such a conditional recovery is of considerable benefit. After all the slavery of refills (if it may be so-called) compares most favorably with the awful slavery of the foul stinking spittoon. Not only did the collapse treatment in those imperfect cases protect the patients against the dangerous complications referred to previously, but it enabled them to lead a normal life, to sustain themselves by their daily work and to be relieved from the social ban caused by a disease which made them repulsive and undesirable. One must not forget that the unfortunate bearer of a bronchiectasis is not seldom made an outcast by his fellow-workers. One of my patients, whose lung could not be collapsed on account of adhesions, finally committed suicide for precisely that reason.

In 13 cases the success of pneumothorax was unconditional, complete, permanent and has lasted up to the present time for three, five, six and eight years after the treatment was stopped. My earliest case, which does not appear in these hospital figures, and whose pneumothorax was induced in January 1914 and abandoned in August of the same year, has now been free of symptoms for nearly 19 years. Not the least interesting feature of these recoveries is the rapid return to a normal shape of the pronouncedly drum-stick shaped fingers, which are so characteristic of bronchiectasis.

It is often claimed that the scope of pneumothorax treatment is limited to bronchiectasis of short duration, especially in children. This may be true in a general way. I wish nevertheless to emphasize the fact that, among my recoveries, figures the case of a boy of nine whose treatment was initiated after he had been ill for seven years, and that of a girl of 20 who had been ill for more than 10 years. Another case concerned a gentleman aged 59, who had been ill for two years. There are therefore exceptions to that assumed rule. Anyhow this should be an inducement to have recourse to pneumothorax treatment as early as possible.

I feel pretty certain that if bronchiectasis were always diagnosed early—as it indeed should be nowadays since the use of iodized oil has proved an infallible method of demonstrating the presence of dilated bronchi—and if the pneumothorax treatment were always initiated as soon as the diagnosis had been established, the proportion of recoveries would increase very substantially. Many years were lost before the necessity of early pneumothorax treatment in ulcerative tuberculosis of the lung was universally admitted. But since it has been admitted, the proportion of successes has become considerably greater than it was in the days when pneumothorax was regarded as an exceptional measure and, so to say, as a last resource. I venture to predict that the pneumothorax treatment of bronchiectasis will be a repetition of the same story.

But there are failures, and there always will be failures, the most usual cause of which is the early formation of symphyseal adhesions. In this conjunction again the lesson which collapse therapy of lung tuberculosis has taught us should not be lost. In other words we should, without loss of time, take advantage of the second best and least harmful form of collapse therapy, namely avulsion of the phrenic nerve. In 11 of my cases of bronchiectasis in which adhesions had caused the failure of pneumothorax, phrenicectomy was performed: three patients made a perfect, complete, permanent recovery, four other patients were greatly improved but not cured. What the proportion may be of patients who, having derived benefit neither from pneumothorax nor from phrenic avulsion, can be notably improved or definitely cured by lobectomy, it is almost impossible to say at the present time. But I shall certainly raise no difference of opinion in this assembly if I confidently assume that whatever the successes of surgery in the treatment of bronchiectasis may be in the future, they will always be associated with the name of Professor Archibald, of the city of Montreal.

Now, it will be asked, how is the healing of the bronchiectatic condition by lung collapse to be interpreted? One who has seen, at autopsy, those bronchial cavities, flattened and distorted as they are, with their thickened, inelastic walls embedded in thickened inflammatory lung tissue, can hardly imagine that collapse could bring back the dilated bronchi to their normal state. It is true that only those cases come to autopsy which have lasted a comparatively great length of time. If we could study the lesions in the earlier phases of the disease, we would probably find them more likely to be favorably influenced by collapse. Nevertheless it sometimes happens that when iodized oil is injected into the bronchial tree of a former patient who has recovered after pneumothorax treatment or phrenic avulsion, the roentgen-ray picture shows evidence of persistent bronchial dilatations. The question therefore arises of what has been really achieved by collapse. I think it is not very difficult to answer that question. Collapse has made an efficient and thorough drainage of the bronchial tree possible and consequently paved the way for a gradual, spontaneous healing of the bronchial, or to be more precise, of the bronchopneumonic infection. I conceive that all the symptoms of bronchiectasis are due to infection and not to dilatation. A non-infected bronchiectasis is an anatomical abnormality. It is not a disease.

BILATERAL SPLANCHNIC NERVE SECTION IN A JUVENILE DIABETIC*

By GEZA DE TAKATS, M D , and G K FENN, M D , *Chicago, Illinois*

ONE of us, with Cuthbert,¹ reported that excision of the celiac ganglion in the dog resulted in a decided and persistent rise in sugar tolerance. Further analysis of the mechanism of the increase in tolerance showed that bilateral adrenal denervation or bilateral splanchnic section gave identical results.² It was suggested in the first paper that the exclusion of sympathetic nerve impulses may bring about either an increased insulin production or a reduction in the insulin requirement. The susceptibility of the dogs to insulin was markedly increased after either of these operations, a fact previously observed by several workers.³

Such a state of diminished insulin requirement and increased insulin susceptibility would be highly desirable in diabetic patients. In previous attempts to increase sugar tolerance in diabetes^{4, 5, 6} it was pointed out that in the severe type of juvenile diabetes, with frequent occurrence of acidosis and coma at the slightest infection or trauma, an operation would be justifiable if nothing but a stabilization of tolerance could be accomplished. Such an object was sought by producing islet-hypertrophy in the ligated tail of the pancreas, which resulted in a decided rise of tolerance in one, and an indefinite temporary rise in a second diabetic child. It was pointed out, however, in previous publications^{4, 5, 6} that such an operation did not strike at the real cause of diabetes, because unless one would be able to protect the new islets from injurious effects of nervous or hormonal origin, the new islets would become exhausted like the original ones.

Resection of splanchnic nerves, while a much used experimental procedure, has been performed but a few times in man. Thus far, most of the studies in regard to technic have been carried out on the cadaver, and transpleural,⁷ supradiaphragmatic,⁸ infra-mediastinal,⁹ and suprarenal¹⁰ approaches have been suggested. A critical summary of splanchnic section for relieving upper abdominal pain has been presented by Alvarez.¹¹ All these operations have been performed either with the object of relieving painful crises (Jean,⁷ Foerster,¹² Mixter and White¹³) or to relieve gastric atony (Pieri¹⁴). The latter has performed unilateral splanchnic resection seven times to increase gastric tone and peristalsis. To our knowledge, splanchnic resection for diabetes has not been performed before.

The depression of sympathico-adrenal function by adrenal denervation, however, has been suggested by Crile in cases of neurocirculatory asthenia, recurrent hyperthyroidism and peptic ulcer.¹⁵ In a personal communication,

* Received for publication April 29, 1933.

From the Department of Surgery and Medicine, Northwestern University Medical School, St. Luke's Hospital, Chicago.

Dr Crile stated that he had also performed this operation for diabetes but could not make any statements as to the results. The Italian surgeons Conati¹⁵ and Ciminata¹⁶ suggested adrenal denervation in diabetes. Conati denervated the left adrenal in a fifty year old marantic diabetic woman, whose blood sugar fell but later returned to a slightly lower than preoperative level. She needed less insulin than before.

Our reason for selecting splanchnic section instead of adrenal denervation to depress sympathico-adrenal function is as follows. The splanchnic nerves control a far larger area than the suprarenal fibers, an increased blood supply to the pancreas may be of benefit. Secondly, the excision of a long segment of both splanchnic nerves may insure lack of regeneration better than section of nerve fibers going to the adrenals. Crile¹⁴ doubts the possibility of regeneration in adrenal nerves, but our animal experiments uniformly indicate a great regenerative power of the splanchnics. It must be admitted that splanchnic section alone does not denervate the adrenals completely, because of the fibers coming to adrenals from the celiac ganglion and the upper lumbar ganglionated trunk. Nevertheless, in our animal experiments,^{1, 2} celiac ganglionectomy, complete adrenal denervation and bilateral splanchnic section gave identical rises in tolerance. For this reason splanchnic resection was selected in the case to be described.

Investigation of the various methods of approach revealed the supra-diaphragmatic, retropleural approach as the most desirable for our purpose. Aside from the advantage of avoiding an intraperitoneal or retroperitoneal operation with the subsequent difficulty of postoperative feeding, the nerves can be exposed at great length above the diaphragm and an excision of two to three centimeters is possible. Observations on the dog indicated that astonishing distances of splanchnic defects can be bridged by regeneration.

In the selection of a suitable patient for such an operation we were guided by the principles discussed in a previous communication⁶ namely, the severe type of juvenile diabetic, with unstable tolerance, and one that has been diabetic for at least two years and controlled for several months previous to operation. As stated by Allen and Wilder,¹⁷ juvenile diabetes starts with unusual severity and with adequate dietary and insulin control the tolerance may gradually improve. The absence of vascular damage, which may occur so early in juvenile diabetes,¹⁸ can be checked by ophthalmoscopy and films of peripheral vessels. Tests to demonstrate the effect of sympathetic depression on the carbohydrate metabolism of the selected patient will be discussed under the comments.

CASE HISTORY

D. H., an 18 year old colored girl, was admitted on October 17, 1932, to St Luke's Hospital. Her great grandmother died of diabetes. She had had whooping cough, chicken-pox and measles. At the age of 12 and again at the age of 15 she had an acute attack of abdominal cramps, became very thin and lost weight. This could hardly have been due to diabetic acidosis as she promptly recovered from both attacks and was quite well until January 1932 when polydipsia and polyuria set in.

She lost 50 pounds in three months, became very nervous, "jumpy" The patient stated that she never liked or ate sweet foods, as they caused abdominal cramps At the end of March 1932, because of frequent colds, a tonsillectomy was done, following which she became drowsy It was at this time that her diabetes was first discovered The CO_2 combining power went down to 26, the blood sugar rose to 430 milligrams per 100 c c She was admitted under the care of one of us (G K F) Two hundred and thirty-five units of insulin were given during the first 15 hours, together with glucose, fluids and caffeine She was finally discharged on a diet of C 100, P 60, F 175, with a glucose value of 151, representing 2311 calories, 35 units of insulin to be given in the morning and 25 units in the evening The glucose-insulin ratio was 2.5 : 1

During the interval between her discharge from the hospital and readmission, the patient was infrequently observed in the out-patient department Because of circumstances beyond control, her regulation, even on this dose of insulin, was insufficient.

She was a fairly well nourished colored girl, rather nervous, but alert Except for a small colloid goiter without accompanying signs of toxicity, no abnormalities were seen, palpated or heard A right lower molar tooth was found to be infected and later extracted While she had had dietary instructions and took her insulin regularly, there was an intermittent spilling of sugar There was no evidence of peripheral vascular change due to diabetes Both diaphragms moved well and the phrenico-costal angles were clear, a point we wished to be sure about, because of the planned supradiaphragmatic approach to the splanchnic nerves The preoperative diet was C 75, P 50, F 150, a glucose value of 120 covered with 40 units of insulin She was, however, not entirely regulated on this regime, and was very unstable

Preoperative studies revealed that ergot definitely depressed the galactose tolerance curve (figure 1) This we took as being suggestive of a sympathetic hyper-

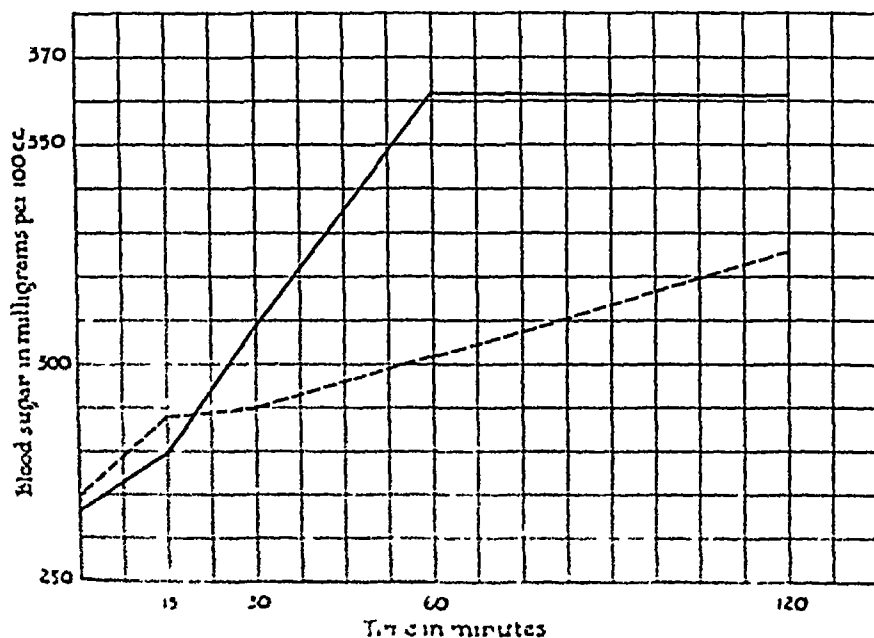


Fig. 1. Galactose hyperglycemia curve. Forty grams of galactose were given in 500 cc of water. Blood sugars were determined by the modified Folin-Wu method at 15, 30, 60 and 120 minutes after the administration of galactose. Straight line—galactose with 0.5 mg of ergotamine. Interrupted line—galactose with 0.5 mg of ergotamine. Note the marked depression of hyperglycemia at one hour.

irritability of the glyco-secretory mechanism. An insulin sensitivity test was run, with the idea of comparing it with others after the operation (figure 2)

After the customary preoperative preparation as required in diabetes⁶ section of the left splanchnic nerves and thoracic chain was done on October 22, 1932. Under ethylene-novocaine anesthesia a left paravertebral incision was made, exposing the eleventh and twelfth ribs and transverse processes. The vertebral ends of the two ribs were resected for a distance of an inch and the transverse processes were bitten off with a double-action bone forceps. The endothoracic fascia was incised and the pleura was peeled away from the lateral surface of the vertebral column, just above the diaphragm. A slight tear occurred in the pleura during this procedure,

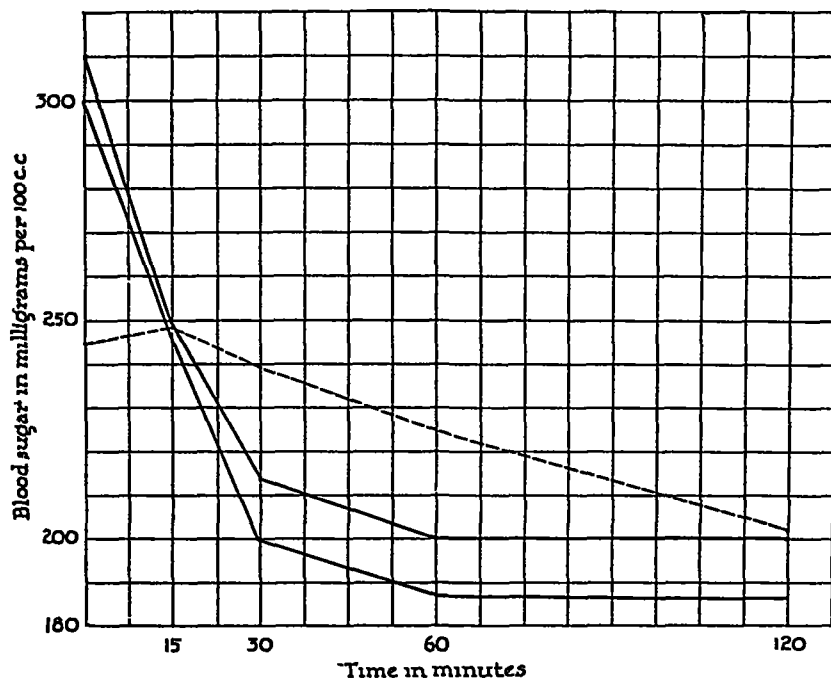


FIG 2 Insulin sensitivity test. One-tenth of a unit of insulin per kilogram body weight was given intravenously and blood sugars were determined by the micro-Folin-Wu method at intervals. Interrupted line preoperative curve. Straight lines postoperative curves taken a month apart. Note the delayed response to insulin before the operation. Following the operation, the blood sugar drops rapidly at 15 and 30 minutes and there is no rise between the first and second hour as if epinephrine response would be inhibited. Urinary sugars taken simultaneously with the blood sugar determinations revealed the renal threshold around 200 milligrams of dextrose in 100 cubic centimeters of blood.

but it was quickly repaired with a fine catgut suture. The left splanchnic nerves and the thoracic sympathetic trunk were picked up with a nerve hook and were sectioned. The long muscles of the back and the lumbodorsal fascia were sutured with interrupted No. 1 chromic catgut sutures. The skin was closed with interrupted silk sutures.

The pulse and general condition of the patient were good at the end of the operation. The pulse was 116 at the start (excitement) and 112 at the end of the operation. There was a slight pneumothorax in the left chest cavity. For the first two days 2,000 c.c. of 5 per cent dextrose and 1,000 c.c. of normal salt solution were given under the skin daily. Insulin was given in doses regulated according to the urinary tests, which were made every four hours. She received from 40 to 45 units of insulin a day. On the third day a soft and on the fifth day a more solid diet was

given, containing 120 grams of available glucose. Severe cramping in the epigastrium was controlled by atropine (gr 1/150) twice a day. The possibility that this represented an exacerbation of an old pancreatitis was considered but ruled out by the low figures for blood-diastase, using a method described elsewhere.¹⁷

The patient made a rapid convalescence. The wound healed by primary intention. With the same diet as before the operation, there was a reduction of the insulin requirement to one-half of the preoperative amount. On November 12, 1932, three weeks after the first operation, the right splanchnic nerves were exposed. The approach was similar, except that the paravertebral incision was continued along the twelfth rib laterally for 6 to 8 centimeters and both skin and musculature were transected. This addition to the original incision facilitated exposure considerably. The vertebral ends of the eleventh and twelfth ribs and the transverse processes were removed. The peeling of the pleura did not result in any tear on this side. The identification of the structures was not as clear, but three definite white strands were cut and removed for a length of three centimeters. Histologic examination revealed one definite nerve trunk. Because of the uncertainty of complete transection, one cubic centimeter of 95 per cent alcohol was deposited in the posterior mediastinum paravertebrally. The wound was closed in layers.

The postoperative convalescence was uneventful. The patient was put on the same diet again with 120 grams of available glucose, and required from 20 to 25 units of insulin. An attempt to discontinue all insulin for a week resulted in the spilling of 49.47, 28.9, 48.15, 63, 75, 71.7, 30, 42.75, and 76.59 grams of glucose on eight successive days. As the patient was nearing coma, insulin was again given and the diet was increased to promote regain of weight. She was discharged on December 19, 1932, on the original preoperative diet of P 50, C 75, F 150, A G 120 and 20 units of insulin. She was seen at intervals and two more insulin sensitivity tests were obtained. Her weight was 114 pounds before operation and had gradually risen to 127 pounds on February 25, 1933. There was no pain or inhibition of motion in the back. (Figure 3)

In addition to studies on insulin sensitivity, blood pressure measurements were taken to see whether splanchnic section might have any depressing effect on blood pressure. No preoperative reading is available. One week after the second operation the blood pressure was 90/68 lying flat in bed. After standing three minutes, blood pressure was 82/62. Five weeks after the operation, blood pressure was

96/80 lying down
86/70 standing five minutes
100/80 after hopping ten times

Fifteen weeks after the second operation, the patient's blood pressure was

110/80 lying down
108/80 standing five minutes
115/80 after hopping ten times

This temporary fall in blood pressure, which is regained after fifteen weeks, closely resembles the experimental findings of Bradford Cannon,²⁰ who found in cats that a progressive removal of the sympathetic ganglionated cord and splanchnic nerves is followed by a fall in blood pressure and then a return to normal. Even completely sympathectomized cats maintained a normal blood pressure.

COMMENT

The operation here described resulted in an abrupt change of the glucose-insulin ratio of the diabetic child from 2.5:1 to 5:1. This change occurred after section of the left splanchnic nerves, whereas the later sectioning of

the right splanchnic nerves did not produce any further improvement. During the postoperative period of four months the patient not only regained her original preoperative weight (114 pounds), but increased it to 129 pounds. It is of some significance that several subsequent attacks of upper respiratory infection did not upset her insulin requirement. This now seems

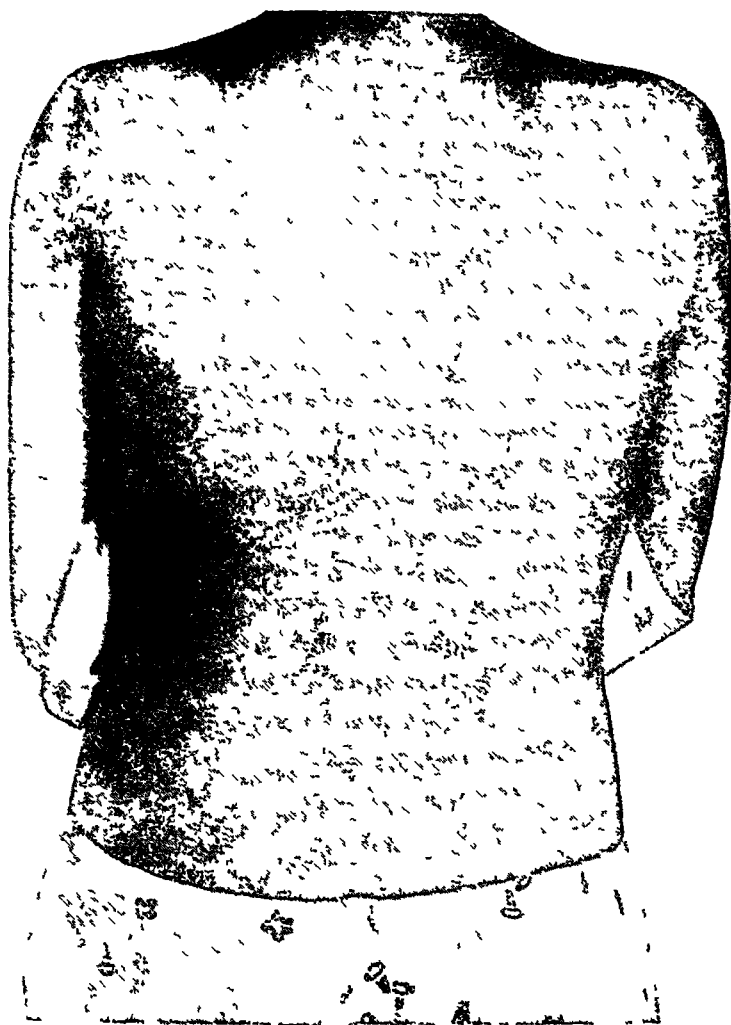


FIG 3 Photograph of patient's back two weeks after second operation. Both incisions healed by primary union. The muscles of the back show no atrophy and there is no limitation of motion and no neuralgia. Note the rectangular incision on the right side, which facilitated exposure.

to be stabilized at 20 to 25 units for a diet of 120 grams of available glucose. We are, of course, aware of the spontaneous fluctuations of tolerance in diabetic patients, and particularly of the improvement of tolerance in hospital-

ized patients, who can be far more closely controlled than the ambulatory ones. In this instance, however, the patient was not controlled after the operation, but on the contrary all insulin was withdrawn for a whole week to see how much the patient's own insulin output had improved. And yet a very definite improvement of the glucose-insulin ratio resulted. The improvement occurred immediately after section of the left splanchnic nerves and did not increase after the section of the right splanchnic nerves. Whether this indicates a predominating influence of the left splanchnic nerves on bilateral adrenal secretion or whether the nerves had not been all severed on the right side cannot be decided at present.

One might assume that there was no increased insulin secretion in this child following the operation, because large quantities of sugar were excreted on the preoperative diet when insulin was discontinued. But the insulin sensitivity of the patient had increased (Figure 2). It will be noted that the preoperative administration of 0.1 of a unit of insulin per kilogram body weight given intravenously produced no drop of blood sugar at 15 and 30 minutes, and even after an hour it had only dropped from 245 milligrams to 225 milligrams, a slight drop of 8 per cent. After the operation, however, the two tolerance curves, which check remarkably well with each other, show a marked drop at 15 and 30 minutes. The average drop at one hour from 305 to 193 milligrams represents a 36.7 per cent drop, and this level is maintained for another hour.

The test for insulin susceptibility can readily separate insulin-resistant patients from those that are insulin sensitive. It is possible that different types of diabetic patients will be thus distinguished from each other, although much experimental and clinical work is yet to be done to establish the value of insulin sensitivity.¹

We have also tried to elicit some objective sign of sympathetic hyperirritability in this patient and, following the suggestion of Pollak,²¹ have administered 40 grams of galactose to the patient, followed by blood sugar determinations. According to this author, 0.5 milligram of ergotamine inhibits the galactose hyperglycemia in one group of diabetics, and it is this type of diabetic we are interested in, in whom the sympathetic depressor action of ergot imitates the surgical effect of splanchnic section. This patient showed a definite inhibition of the galactose hyperglycemia, following the subcutaneous administration of ergot (Figure 1). At present we are engaged in other tests which would imitate the effect of a bilateral splanchnic section on a blood sugar curve.

What the discovery of insulin has meant to the diabetic, but particularly to the diabetic child, has been repeatedly emphasized.^{15, 16} Juvenile diabetes before the insulin era was almost always fatal. Unfortunately, however, the low mortality statistics of Joslin, Wilder and Allen, and Priscilla White cannot be reproduced in the country at large. Wilder²² has recently stated that the death rate from diabetes is actually mounting and that diabetic patients throughout the country are either not using insulin or not using it

properly In Ontario, where insulin is provided free of charge to charity patients, none had been used in 44 per cent of 192 cases of fatal diabetes and in only 12 per cent had it been used with any regularity²¹ In Oregon, only one of two patients who died of diabetes used insulin at any time, only one in four used it in the final illness, and only one out of three knew how to test for sugar in the urine In this state only 15 per cent of the fatal cases had ever used insulin regularly,²² and in the state of Washington, only 16.5 per cent used it²³ The actuarial statistics of the Metropolitan Life Insurance Company portray a very sad picture of diabetic mortality (cit by Wilder²²) The physical surroundings and the economic difficulties of certain types of diabetic children are such that an adequate dietary and insulin control is not feasible Thus in addition to other considerations, a definite social and economic indication must be recognized in the selection of diabetic children for operation

The present report is considered as a preliminary step toward a thorough investigation of various types of juvenile diabetic patients A patient with a severe type of uncomplicated juvenile diabetes, who was poorly controlled but had not yet developed detectable vascular damage and in whom a suppression of sympathetic glyco-secretory discharge could be accomplished with ergot, has proved to show stabilization and improvement following splanchnic nerve section* Her insulin resistance has been modified Only a careful selection of future cases, with observations over a prolonged period of time, will establish the value of this operation

SUMMARY

Bilateral splanchnic section was performed on an 18 year old diabetic girl with the purpose of stabilizing and increasing her sugar tolerance There has been an immediate drop to one-half of her previous insulin requirement, which seems to be due to an increase in insulin sensitivity and which has persisted up to the present writing, four months after the operation Further studies with a final report will be made at a later date

BIBLIOGRAPHY

- 1 DE TAKATS, G, and CUTHBERT, F P Effect of celiac ganglionectomy on sugar tolerance of dogs, *Am Jr Physiol*, 1932, **cii**, 614-619
- 2 Unpublished data
- 3 Lit sec, DE TAKATS, G, and CUTHBERT, F P Surgical attempts to increase sugar tolerance, *Arch Surg*, 1933, **xxvi**, 750-764
- 4 DE TAKATS, G, and WILDER, R M Isolation of tail of pancreas in diabetic child, *Jr Am Med Assoc*, 1929, **xciii**, 606-610

* Nine months after operation the daily insulin requirement is still 20 units The fasting blood sugars are between 120 and 146 mg per 100 c.c Without our knowledge the patient married in the meantime and is now in the fourth month of pregnancy The effect of pregnancy on her tolerance will be followed and reported later At present, her diabetes is stable, mild, easily controlled A second diabetic child, recently operated upon, made a smooth postoperative convalescence

- 5 DE TAKATS, G Ligation of tail of pancreas in juvenile diabetes, *Endocrinology*, 1930, xiv, 255-264
- 6 DE TAKATS, G Effect of ligating tail of pancreas in juvenile diabetes, *Surg, Gynec and Obst*, 1931, lxi, 45-53
- 7 JEAN, G Essai sur la chirurgie des crises gastriques du tabes, *Lyon chir*, 1921, xviii, 339-350
- 8 PIERI, G La cura chirurgica della nevrosi gastriche, Belluno, Topografia Editrice "La Cartolibraria" 1930
- 9 ROSSI, F La resezione del tronco simpatico toracico e dei nervi splanchnici nello spatium inframediastinale posterius, *Arch ital di chir*, 1928, xxi, 729-740
- 10 PEREIRA, A DE S Nervi splanchnici, contribucao para o estudo de anatomia e cirurgia dos nervos esplancnicos, Tipografia Porto Medico, Porto, 1929
- 11 ALVAREZ, W C Abdominal pain, paths over which it travels and ways in which these may be blocked, *Am Jr Surg*, 1931, xiv, 385-394
- 12 FOERSTER, O Die Leitungsbahnen des Schmerzgefuhrs und die chirurgische Behandlung der Schmerzzustande, 1927, Urban und Schwarzenberg, Berlin
- 13 MIXTER, J Y, and WHITE, J C Pain pathways in sympathetic nervous system, *Arch Neurol and Psychiat*, 1931, xxv, 986-997
- 14 CRILF, G W Recurrent hyperthyroidism, neurocirculatory asthenia and peptic ulcer, treatment by operations on suprarenal-sympathetic system, *Jr Am Med Assoc*, 1931, xcvi, 1616-1618 Denervation of adrenal glands for neurocirculatory asthenia, technic and clinical results, *Surg, Gynec and Obst*, 1932, liv, 294-298
- 15 DONATI, M Tentativo di trattamento chirurgico del diabete con la enervazione di una capsula surrenale, *Arch ital di chir*, 1929, xxiv, 357-361
- 16 CIMINATA, A Einfluss der Durchschneidung der Nebennieren auf den Diabetes mellitus, weitere Beitrage, *Klin Wchnschr*, 1932, xi, 150-153
- 17 ALLEN, F N, and WILDER R M Causes of failure in treatment of diabetes of children, *Jr Am Med Assoc*, 1930, xciv, 147-152
- 18 WHITE, P Diabetes in childhood and adolescence, 1932, Lea and Febiger, Philadelphia
- 19 DE TAKATS, G, and MACKENZIE, W D Acute pancreatic necrosis and its sequelae, critical study of 30 cases, *Ann Surg*, 1932, xcvi, 418-440
- 20 CANNON, B Effects of progressive sympathectomy on blood pressure, *Am Jr Physiol*, 1931, xcvi, 592-596
- 21 POITAK, L Untersuchungen zur Pathogenese des Diabetes mellitus, *Wien klin Wchnschr* 1932, xlv, 251-263
- 22 WILDER, R M Ten years' experience with insulin, *Lancet*, 1932, ii, 535-538
- 23 DEFRIES R D, and ROSS, M A Analysis of 192 deaths attributed to diabetes in Ontario with special reference to insulin, *Can Public Health Jr*, 1930, xxi, 558-566
- 24 HOLCOMB, B Deaths attributed to diabetes in Oregon, study of 168 cases with special reference to insulin, *Northwest Med*, 1932, xxxi, 14-17
- 25 PATTER, L J Is insulin reducing diabetic mortality? Conclusions from study of diabetic deaths in Washington in 1929, *Northwest Med*, 1931, xxx, 319-322

CHRONIC ARTERIAL OCCLUSION OF THE EXTREMITIES *

By DUNCAN GRAHAM, M B (Tor), F R C P (C), *Toronto, Ontario,
Canada*

CLINICIANS have long recognized that certain conditions, usually of a chronic nature, which affect the extremities and commonly terminate in gangrene, result from insufficient circulation. With the demonstration by Raynaud that gangrene could develop without vascular occlusion, these conditions were divided into two groups (1) those due to structural disease of the arteries, described and classified under the general term arteriosclerosis, (2) those due to functional disturbance of the arteries without structural change for example, Raynaud's disease. The accepted neurogenic origin of the vascular disturbance in Raynaud's disease and in the condition described later by Weir Mitchell as erythromelalgia and the similarity of many of their symptoms to those found in certain purely nervous conditions have caused them to be described and classified among diseases of the nervous system under the heading of vasomotor and trophic neuroses. As a result, both these conditions have attracted the attention of the neurologist rather than of the clinician interested in cardiovascular disease. The demonstration by Buerger¹ of the nature of one form of structural vascular disturbance, namely, thromboangitis obliterans, and his later publication of a textbook on "Circulatory Disturbances of the Extremities"² have been distinct contributions to our knowledge of vascular affections of the extremities. Buerger was one of the first to apply in a systematic manner the new knowledge concerning the physiology of the capillary system to the study of peripheral vascular disturbances, and to stress its value in diagnosis. With the limited exact knowledge available up to that time of the normal function and control of the capillary system, it is not surprising that in clinical textbooks little or no mention was made of the rôle of the capillaries in circulatory disturbances. Thanks to the studies on the anatomy and physiology of the capillaries, particularly to those of Krogh³ and his pupils, and to the work of Lewis⁴ and his associates on the response of the blood vessels of the human skin, it has become possible for clinicians to interpret more intelligently the abnormal changes occurring in the skin following disturbances in the circulation, and to appreciate more fully their significance in the diagnosis and treatment of vascular affections.

It would appear fortunate that, at this stage in the development of our knowledge the operation of ganglionic sympathectomy was introduced by the surgeon as a means of treatment for increasing the blood flow to extremities affected by vascular disease. Being a therapeutic measure, it

* Read before The American College of Physicians, Montreal, February 10, 1933

stimulated a wider interest among clinicians, both physicians and surgeons, in peripheral vascular disturbances. A number of workers, notably Lewis,⁵ Brown and Adson,⁶ White,⁷ Scott and Morton,⁸ to mention only a few, have made carefully controlled observations before and after sympathectomy on patients suffering from different types of vascular disturbance. These investigations have given us a better and clearer understanding of the nature and origin of circulatory disturbances occurring in the extremities.

When one reviews the present situation, it is observed that no new type of vascular disease has been found since Buerger gave us a pathological and clinical description of thromboangitis obliterans, and that no change has been made in the classification of peripheral vascular disease into two main groups—one, organic or obliterative, the other, functional or vasomotor. The clinical manifestations, however, have become fairly well defined and one has a much clearer conception of the causal relationship of functional disturbances in different parts of the vascular system to the production of the symptoms and signs present in various types of peripheral vascular disease. With our present knowledge and methods for the examination of the circulatory efficiency of the extremities, the different types of vascular disease can be accurately diagnosed and, in the majority of cases, this can be accomplished by the regular bedside or office methods of examination. As yet, proficiency in accurate diagnosis is confined largely to those especially interested in local vascular disturbances. Failure to make a correct diagnosis is common and is due chiefly to a lack of appreciation of the diagnostic significance of the local signs and symptoms associated with disturbances of function of the peripheral vascular system from the small arteries to the venules. There may also be failure to recognize that functional vascular disturbances are often prominent in the obliterative type of vascular disease. Much confusion in diagnosis would disappear if physicians generally took a keener interest in the significance of these disturbances and if writers of textbooks of medicine would direct the attention of the reader to the vascular origin of Raynaud's disease, erythromelalgia, and allied vascular disturbances by discussing them under vascular disease rather than under vasomotor and trophic neuroses of the nervous system. In a recent textbook of medicine, this change in the usual classification has been adopted.⁹

In suggesting that Raynaud's disease and erythromelalgia be classified as vascular disease rather than disease of the nervous system, I am not unmindful of the fact that many of the local subjective symptoms and many of the changes occurring in the skin and subcutaneous tissue, found in these conditions, are present in certain primary diseases of the nervous system, and may be considered adequate justification for their classification under this system. However, it is becoming more and more evident that trophic disturbances, and probably many of the peripheral symptoms found in primary lesions of the nervous system, are of vascular rather than of nervous origin. The fact that cases of Raynaud's disease, with or without sclerodactylitis, experience relief of symptoms and show improvement of the trophic

changes in the skin and subcutaneous tissue following sympathectomy indicates that interference with the normal blood flow plays an important, if not the essential, rôle in their production. In support of this view is the favorable influence of increased blood flow following sympathectomy on trophic changes and possibly on the growth of the limb in poliomyelitis (Harris¹⁰), and on the healing of perforating ulcer in degenerative lesions of the nervous system (Fraser¹¹). Further, it would appear that sclerotic vascular changes are responsible not only for the well known obliterative vascular disturbances in diabetes mellitus, but are the primary cause of the symptoms of peripheral neuritis, if present (Woltman and Wilder¹²). Is this not adequate justification for a more conscious recognition by clinicians generally of the vascular origin of nutritional disturbances and of many symptoms occurring in the extremities in certain diseases primarily affecting the nervous system?

As to the nature of the lesions in different types of peripheral vascular disease, structural changes of the arteries in the obliterative group and vasospasm or vasodilatation in the functional group are the immediate causes of the circulatory disturbances. The common clinical conditions belonging to the obliterative group are thromboangitis obliterans and peripheral arteriosclerosis of advancing years or occurring with diabetes mellitus. The vascular changes in thromboangitis obliterans, as demonstrated by Buerger, have a definite character quite distinct from those found in peripheral arteriosclerosis. The early lesion is an inflammation of the wall of the larger arteries, chiefly of the lower extremity, beginning in the adventitia and involving all coats of the vessel, finally causing thrombosis followed by organization and canalization. The lesions are multiple, affecting different segments of the vessels, and in the examination of an amputated limb different lesions are found to show varying stages of acute and chronic inflammation. While the veins may be involved in a similar process, disease of the arteries with occlusion is the chief and primary cause of the circulatory disturbances.

Unless sudden occlusion of a vessel occurs, circulatory disturbances may be absent in the early course of the disease. If the part affected is subjected to exercise, the first complaint is fatigue and aching upon exertion, later, the pain of intermittent claudication develops, which we now know to be due, not to spasm of the artery, but to chemical changes occurring in the muscle resulting from a deficient blood supply. Vasospastic or functional disturbances may occur at this stage: numbness, tingling, and sensitivity to cold causing pallor or cyanosis. In some cases these symptoms may be more or less prominent and lead to the erroneous diagnosis of Raynaud's disease. Coldness is present and, in the dependent position, rubor of the distal parts develops, and pallor in the elevated position. The capillaries are dilated and partially paralyzed.

With the diminution of the blood supply to the minute vessels of the skin, nutritional or trophic changes in the skin and nails develop. As is

found in peripheral arteriosclerosis, external trauma plays an important rôle in accelerating the development of these changes and finally causes ulceration and gangrene. After nutritional changes make their appearance, the most distressing symptom for the patient is the pain which occurs in the distal parts of the extremity during rest. It may occur without the appearance of ulceration or gangrene. Metabolic changes in the tissues, resulting from deficient circulation, rather than involvement of the nerves in the perivascular inflammation at the site of the lesion, would appear to be the chief cause of rest pain. Edema may occur due to occlusion of the veins or from posture in the later stages of the disease. In thromboangitis obliterans the important clinical manifestations are pain of intermittent claudication, postural color changes, coldness, peripheral nutritional changes in the skin and nails, rest pain, and absence of pulsation in palpable arteries distal to the arterial occlusion. These symptoms develop as a result of occlusion of a large artery, or arteries, of the extremity.

In the arteriosclerotic type of vascular disturbance, occlusion of one or more arteries of the size commonly affected in thromboangitis obliterans has been given as the chief cause of the disturbances resulting from the defective peripheral circulation. When one compares the character and distribution of the arteriosclerotic lesions in the peripheral arteries with those found in thromboangitis obliterans not complicated by arteriosclerosis,—the poor collateral circulation in arteriosclerosis and the relatively good one in thromboangitis obliterans following occlusion—it is difficult to accept occlusion of a large artery as the chief cause of the clinical manifestations in peripheral arteriosclerotic disease.

In the larger arteries of the leg, the primary lesion in arteriosclerosis is a medial degeneration with later calcification producing the beaded type of artery often found on palpation of the radial. The arteries usually affected are the femoral, popliteal, peroneal and radial, less often, the tibial and brachial, and very rarely, the dorsalis pedis. This degeneration of the media impairs the elasticity of the vessel and its lumen becomes larger than normal (Klotz¹³). Intimal thickening may develop as a secondary process but does not cause any significant occlusion unless thrombosis occurs. However, in the branches of these arteries supplying the muscles, bone and skin, intimal thickening without significant medial change develops as a primary process and produces partial occlusion of the main small branches and partial or complete obliteration of their more distal portions. Just as thickening of the intima in the renal artery and its main branches may narrow the lumen and lead to nutritional changes in the kidney, atrophy of muscles and skin may follow similar changes in the smaller arteries of the limb.

In this connection, I recall very vividly an incident which happened during my last visit to the late Sir James Mackenzie. He picked up the thin skin on the back of his hand, and said "What causes that?" Let me quote from his textbook on angina pectoris: "If we wish to grasp the meaning of the nature and significance of a great many symptoms of dis-

ease, we should look at the changes that occur in the progress of the healthy man from the cradle to the grave" Again "A great many symptoms of disease owe their production to the impaired function of organs brought about by the diminution of their capillary field. Accompanying this, and probably causing it, are the diseased arteries. To appreciate these vascular changes we have but to compare the condition of the skin of an elderly man with that of a youth. In the latter the skin is of a thick velvety consistence, well supplied with blood, in the former case the skin is thin and attenuated, sometimes resembling tissue-paper and almost bloodless" ¹⁴

The absence of these nutritional changes in cases of thromboangitis obliterans not complicated by arteriosclerosis, and in certain elderly individuals showing marked beading of the radials, strongly suggests that intimal changes in the smaller arteries, rather than thrombosis of a large artery or medial degeneration with intimal thickening causing partial occlusion, are responsible for peripheral atrophic changes in arteriosclerosis. In thromboangitis obliterans intimal changes are absent in the small arteries and a good collateral circulation develops following thrombosis of a larger artery. Even if one admits that a gradual narrowing of the lumen of the larger arteries develops from intimal thickening, one cannot explain the poor collateral circulation that is characteristic of the arteriosclerotic type of peripheral vascular disease without taking into account some additional factor, such as intimal thickening of the smaller arteries, which would cause a definite diminution in the blood flow to the muscles and the skin. Further, the incidence of intermittent claudication should be much higher in arteriosclerosis than in thromboangitis obliterans, owing to the poorer collateral circulation in the former, but such is not the case. For these reasons, it would appear that partial occlusion of the smaller arteries rather than occlusion of the larger arteries is the chief and primary cause of the arteriosclerotic type of vascular disturbance.

The arteriosclerosis of advancing years and that associated with diabetes mellitus are apparently of the same type and affect vessels of the same size. While this is true, there is a difference between the skin of the patient who develops signs of peripheral arteriosclerosis during diabetes mellitus and the skin of one who develops diabetes mellitus after definite signs of peripheral arteriosclerosis have appeared. When diffuse atrophic changes are found in the skin of an arteriosclerotic diabetic, one may conclude that the diabetes mellitus was a later development. In the majority of diabetic patients, however, these advanced changes are absent and the skin over the dorsum of the foot is normal for the age of the patient. On the other hand, the skin over the dorsum of the toes, more commonly the great and second toes, may be found to be slightly thickened, wrinkled and less elastic than normal, or more marked thickening along the nail fold or under the end of the nail may be present, with the nail brittle and thickened. Calluses over the ball of the foot are not uncommon. These changes are the early nutritional manifestations of peripheral arteriosclerosis and minimal traumata.

are the likely cause of their local distribution. After a slight abrasion, often caused by paring a corn or callus, infection develops, thrombosis of the small arteries occurs, causing necrosis and gangrene. In diabetic gangrene pulsation of the *dorsalis pedis* is usually present.

In the senile arteriosclerotic, the nutritional changes in the skin described above may be accompanied by increasing intolerance to cold and acroparesthesia. On palpation, pulsation in the *dorsalis pedis* is diminished or absent. Complaints of fatigue or aching pains in the legs with exercise, or crampy pains occurring more often during the night are not infrequent. Intermittent claudication, that is pain on exercise and quickly relieved by rest, occurs but, in our experience, is not commonly complained of by the patient. With progressive occlusion of the small arteries of the foot, the process may terminate in a dry, withering gangrene of part of the foot. Repeated minimal traumata from exposure to cold, hot water bottles, ill fitting boots, slight crushing, etc., would appear to be the factors causing the localization of the necrosis and gangrene to one or more toes or a small portion of the foot. If the trauma is more severe, or if infection develops through a small abrasion, thrombosis of the partially occluded arteries develops and a moist gangrene is the result. Should a large artery become thrombosed, persistent pain usually develops near the site of the occlusion, the distal parts become cold, pale or cyanosed and, with the lack of development of an effective collateral circulation, a large area of gangrene appears.

In all types of obliterative vascular disease, students of the subject stress the importance of mild external trauma as a precipitating factor in the development of gangrene, and in the treatment of diabetes mellitus special attention is given to the care and protection of the feet as a means towards its prevention. More severe trauma may injure even healthy tissues and cause thrombosis of small arteries and capillaries, but whether the results of minimal traumata on parts with a defective circulation are due to further damage of tissues or vessels, or both, has not been determined. In the obliterative type of vascular disease, the suggestion has just been advanced that repeated minimal traumata, of a type and severity to cause no disturbance to a digit with normal circulation and sensation, are responsible for the localization of gangrene to one or two digits in a foot in which there is diminution in the blood supply to the whole foot. It is a significant fact that, not only in the obliterative type but in the vasospastic type of vascular disturbance, one or two digits are apt to be more severely affected than the other three. In Raynaud's disease, the bilateral and often symmetrical distribution of the vasospastic disturbance is recognized. Nevertheless, one or more digits usually show more marked changes than the others, and following sympathectomy recovery in these is less complete or less permanent. Is it possible that repeated minimal traumata, chiefly due to exposure to cold, are responsible for the localization of the more severe changes found in certain digits in Raynaud's disease? Recently Lewis has challenged the original and generally accepted view of Raynaud that this disease is a vaso-

neurosis and that the vasospastic disturbances are due to a fault in vasomotor innervation of distant rather than of local origin in the part affected. From his carefully controlled experiments on cases of Raynaud's disease, Lewis came to the conclusion that spasm of the vessels is due, not to abnormal vasomotor impulses, but to a local vascular fault. In milder forms this defect is expressed as a susceptibility to enter a state of spasm; in the more severe forms, spasm is reinforced by local structural change. In referring to the primary cause of the spasm, he states "In searching for the determining cause of spasm, we must review the several possibilities and ascertain whether the abnormality is local or lies at a distance, it will not be found in both. Our conclusion is that the cause is a local cause." Lewis admits that vasomotor impulses play a part in the vasospastic disturbances, but contends that the effect is due to the action of normal rather than abnormal impulses in a vessel with a local vascular fault, the exact nature of which is at present unknown. In an attempt to test these two hypotheses, Levy-Simpson, Brown and Adson¹⁵ investigated eight cases of Raynaud's disease, using methods similar to those of Lewis. They concluded that the preponderance of their experimental evidence confirmed Raynaud's original view of the abnormality of the sympathetic nervous system. In one of the eight cases studied, a primary local vascular fault could not be excluded as the cause of the vascular spasm. As pointed out by these authors, Lewis' evidence of a local vascular fault as the primary cause of spasm has been based chiefly on experimental observation on cases of Raynaud's disease affecting the upper extremities and showing definite nutritional changes or gangrene of the tips of the fingers. It is generally recognized that the clinical results following sympathectomy in Raynaud's disease are more satisfactory in the lower extremity than in the upper, and better and more complete in mild than in severe forms of the disease. More evidence of a local vascular fault in mild forms of Raynaud's disease is necessary, therefore, before this can be accepted and a vasomotor origin discarded as the primary cause of spasm.

The observations of Stopford and Telford on cases of cervical rib with unilateral vascular complications should not be overlooked in a consideration of the primary cause of vasospastic disturbances. Some years ago, Stopford¹⁶ reported that paralysis of vasomotor fibers never seemed to induce vascular changes but that partial division and irritation of peripheral nerves had been found on several occasions to be succeeded by vascular changes. The vascular lesion found was a thickening of the intima, most marked in the smaller arteries in the distal part of the extremity. More recently, Telford and Stopford¹⁷ have demonstrated, to their own satisfaction at least, that the vascular complications of cervical rib are due to irritation of the vasoconstrictor fibers in the lower branch of the brachial plexus. Stopford states that he is convinced that long continued irritation of the vasoconstrictor fibers is the primary cause of the changes in the arterial wall. These observations have a double interest in suggesting that long continued irritation of vasoconstrictor fibers may be the cause, not only of vasospastic

disturbances similar to Raynaud's disease, but of the development of structural changes in the arteries. While it is impossible at the present time to express any final opinion as to the primary cause of spasm in Raynaud's disease, it is agreed that spasm of the smaller arteries is the primary cause of the vascular disturbances. It would appear reasonably certain that structural changes in the vessels are responsible for the advanced nutritional changes characteristic of the more severe forms of Raynaud's disease. No adequate explanation has been offered for the appearance of more marked changes in certain digits. The suggestion that repeated minimal traumata are responsible seems a reasonable one.

BIBLIOGRAPHY

- 1 BUEGER, L. Thromboangitis obliterans: a study of the vascular lesions leading to presenile spontaneous gangrene, *Am Jr Med Sci*, 1908, cxxxvi, 567-580.
- 2 BUEGER, L. The circulatory disturbances of the extremities, including gangrene, vasomotor, and trophic disorders, 1924, W. B. Saunders Co., Philadelphia.
- 3 KROGH, A. The anatomy and physiology of capillaries, 1922, Yale University Press, New Haven.
- 4 LEWIS, T. The blood vessels of the human skin and their responses, 1927, Shaw and Sons, London.
- 5 LEWIS, T. Angina pectoris associated with high blood pressure and its relief by amyl nitrite, with note on Nothnagel's syndrome, *Heart*, 1931, xv, 305-327—Supplementary notes upon reactions of vessels of human skin to cold, *ibid*, 351-358.
- 6 BROWN, G. E., ADSON, A. W., et al. Collected papers of The Mayo Clinic and The Mayo Foundation, 1927-1930.
BROWN, G. E., ALLEN, E. V., and MAHORNER, H. R. Thromboangitis obliterans: clinical, physiologic and pathologic studies, 1928, W. B. Saunders, Philadelphia.
- 7 WHITE, J. C. Progress in surgery of sympathetic nervous system, *New England Jr Med*, 1931, ccv, 449-455—Raynaud's disease, studies on postoperative cases bearing on etiology of disease and efficiency of sympathetic ganglionectomy, *ibid*, 1932, ccvi, 1198-1210.
- 8 SCOTT, W. J. M., and MORTON, J. J. Sympathetic activity in certain diseases, especially those of peripheral circulation (Mary Scott Newbold lecture), *Arch Int Med*, 1931, xlviii, 1065-1097.
- 9 BROWN, G. E., in MUSSER, J. H. Internal medicine: its theory and practice, 1932, Lea and Febiger, Philadelphia.
- 10 HARRIS, R. I. Personal communication.
- 11 LEVY, J. Autonomic nervous system in relation to surgery, *Trans Med-Chir Soc Edinburgh* 1930-1931, pp. 189-214.
- 12 WOLFE, H. W., and WILDER, R. M. Diabetes mellitus, pathologic changes in spinal cord and peripheral nerves, *Arch Int Med*, 1929, xlv, 576-603.
- 13 KLOTZ, O. Concerning the pathology of some arterial diseases, *Ann Clin Med*, 1925-1926, vi, 814-828.
- 14 MACEVOY, J. Angina pectoris, 1923, H. Frowde, Hodder and Stoughton, London.
- 15 LEVY, J., SUTTON, S., BROWN, G. E., and ADSON, A. W. Raynaud's disease, evidence that it is due to vasomotor neurosis, *Arch Neurol and Psychiat*, 1931, xvi, 687-718.
- 16 SUTTON, J. S. B. A preliminary note on the trophic disturbances in gunshot injuries of the peripheral nerves, *Lancet*, 1928, i, 465-467—The pathological diagnosis in gunshot injuries of the peripheral nerves, *ibid*, ii, 445-448.
- 17 LEVY, J., and SUTTON, J. S. B. Vascular complications of cervical rib, *Brit Med J*, 1931, ii, 557-564.

THE DIAGNOSTIC USE OF IODINE IN THYROTOXICOSIS*

By J H MEANS, M D , F A C P , *Boston, Massachusetts*

THREE years ago at the Minneapolis Meeting of the College a paper was presented by the author on the use of iodine in exophthalmic goiter¹ The discussion then centered chiefly about the therapeutic use of that agent However, because of its utterly characteristic action in thyrotoxicosis the use of iodine may also give diagnostic information of great importance, in cases where the presence or absence of thyrotoxicosis is in doubt

The chief questions which a doctor must decide, when confronted with a patient with a goiter, are whether this goiter is accompanied by hyperfunction, whether it is causing pressure, or whether it is malignant, premalignant, or inflammatory

The symptoms of hyperfunction are familiar to you, and ordinarily the diagnosis of this disturbance is thoroughly simple However, this is not always so A number of conditions may resemble mild thyrotoxicosis, and in such cases single or scattered determinations of the basal metabolism may fail to prove whether thyrotoxicosis is truly present In this class come patients with goiter which may be either colloid or hyperplastic, and with symptoms which may be due either to hyperthyroidism or to psychoneurosis The older writers had much to say of atypical types of Basedow's disease *Formes frustes* was the euphonious name given them It is our belief that cases running an atypical course throughout are rare However, when the disease is just beginning the picture may be sufficiently incomplete to cause confusion, and it is true also that in the older patients with toxic goiter the symptoms may suggest heart disease far more than thyrotoxicosis In all of such cases the diagnostic use of iodine is helpful It has also been stressed in the literature that tuberculosis may present a picture like mild thyrotoxicosis This problem in differentiation, however, has not loomed large in our own experience at the Massachusetts General Hospital

I may also mention the great group of patients who have received treatment, either surgical or roentgenological, for known toxic goiter, and who, following such treatment, may or may not have a remnant of thyrotoxicosis smouldering on A diagnostic test with iodine in this group is often decidedly helpful in the accurate estimation of the clinical status Indeed we have taken the stand that the final criterion of complete cure in toxic goiter is freedom from symptoms, and a metabolic rate not above standard, which is uninfluenced by iodine

Diagnostic tests with iodine for all these purposes we have made with steadily increasing frequency in our clinic I should like to illustrate to you

* Read at the Montreal Meeting of the American College of Physicians, February 6 1933
From the Thyroid Clinic of the Massachusetts General Hospital

some of the ways in which they have been helpful First of all the importance of accurate observation must be emphasized Single or infrequent determinations of metabolic rate in these doubtful cases tell us very little It has been found necessary to establish levels of metabolism, to determine trends

Our conception of the action of iodine in toxic goiter has been stated before It is that at any one moment iodine diminishes, to a certain extent, the intensity of the toxemia It has no effect on the duration or direction of the disease

We may represent diagrammatically the metabolic effects which might occur in untreated toxic goiter upon the giving of, and omitting of, iodine medication as in figure 1 Here a prompt fall in basal metabolic rate is

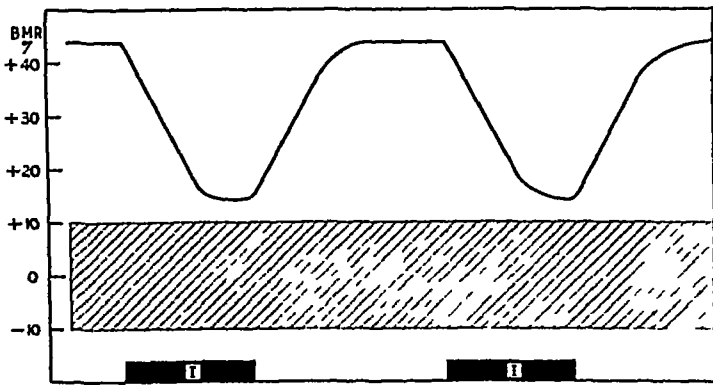


Fig 1 Diagrammatic representation of the effect of iodine in thyrotoxicosis of moderate severity

shown upon the giving of iodine, followed by a rise when the drug is stopped When iodine is given and omitted for the second time the events are repeated

In figure 2 much the same thing is depicted, only in this diagram the dis-

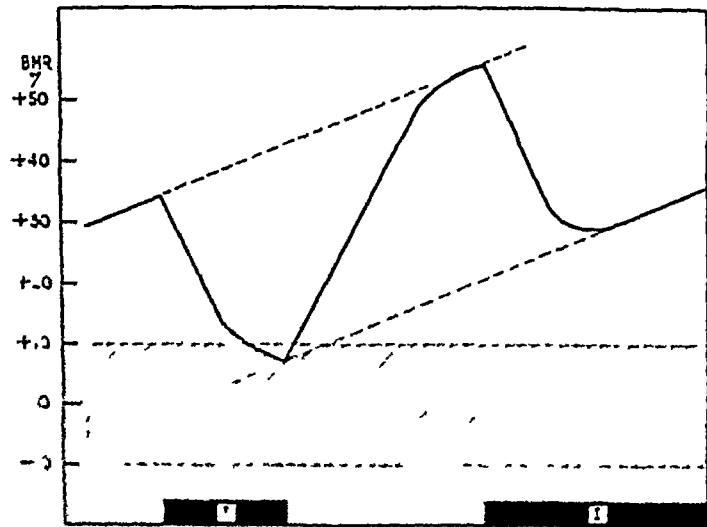


Fig 2 Diagrammatic representation of the effect of iodine in thyrotoxicosis at a time when the disease is increasing in intensity The upper interrupted slanting line indicates the course of the disease when the patient is not receiving iodine, the lower interrupted line shows the patient is under full iodine control

ease is represented as on the upward course so that when iodine is omitted there is a rise of metabolism to a higher level than that obtained before it was given, and when it is given for a second time the level reached is not as low as that reached in the first administration

These two diagrams merely represent the usual iodine relationships. There would seldom be any necessity for a diagnostic test with iodine with the initial basal metabolic rate lying at the level shown. Let us pass, however, to figure 3. Here we have at the start a basal rate little, if at all, above

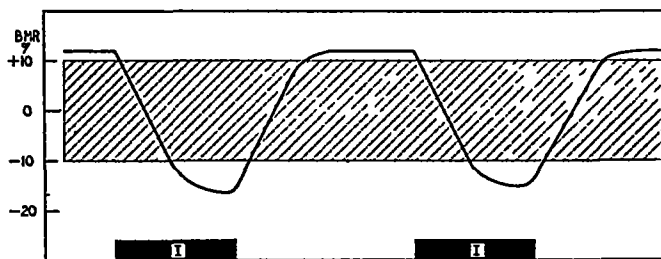


FIG 3 Diagrammatic representation of iodine relationships in a case of genuine thyrotoxicosis but with initial metabolism little if at all above the standard zone. The fluctuations are diagnostic of thyrotoxicosis although the actual initial level would not be diagnostic of that state.

the standard level. The diagnosis is in doubt. Iodine is given. The metabolism falls to slightly below standard. Iodine is omitted. Metabolism rises to the previous level. Iodine is given again and omitted again. The events are repeated. Such fluctuations, in relation to iodine, may be taken as final proof of the existence of thyrotoxicosis, even though the rate never rises above what we call standard.

Figure 4 represents the same events taking place after operation, proving

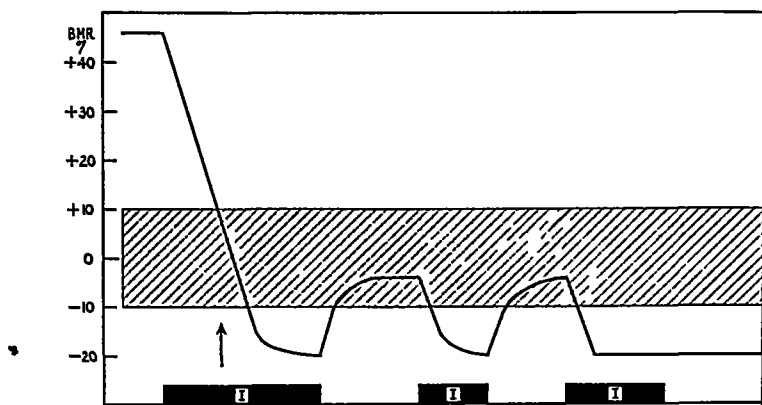


FIG 4 Diagrammatic representation of iodine fluctuations following operation with a rate never exceeding normal. Time of operation is indicated by the arrow. Fluctuations prove that there is an element of active thyrotoxicosis still present.

that an element of thyrotoxicosis remains. Finally the time comes when no rise occurs when iodine is stopped. When this happens thyrotoxicosis has ceased, just as in rheumatic infection when no rise of temperature, white cells, or return of symptoms occurs when salicylate is stopped, we consider that active infection is over.

I should like to devote the rest of the space to some actual examples of the value of the diagnostic use of iodine

First, an Italian girl of fifteen (Mary G) with, when first seen, a goiter which we took to be colloid, and not much in the way of symptoms (This case has been presented in detail in another paper²) The basal metabolism had a level not above normal My colleague, Dr J Lerman, was impressed with the hardness of the gland He believed it had the feel of hyperplastic tissue We gave iodine The basal metabolic rate dropped 27 points We omitted it and the basal metabolic rate rose to the previous level We gave iodine again, got a second drop, took out the thyroid and found it hyperplastic The test with iodine made the diagnosis here It is interesting that it was first suggested by the feel of the gland Here then was a patient with genuine thyrotoxicosis and yet a "normal" level of metabolism

The next case is also that of an Italian—a married woman who was nineteen years of age when we first saw her in January 1927 (Mrs T) At that time there were some symptoms of slight nervousness and sweating and a slightly full, soft thyroid without other signs Our impression was colloid goiter She reported for observation in June of that year and we could find no clinical evidence of thyroid disease

She turned up again in July 1930 She had had a psychic trauma and claimed to be very nervous but we could find very little evidence suggesting thyrotoxicosis The basal metabolic rate on two occasions was in the plus twenties (Figure 5)

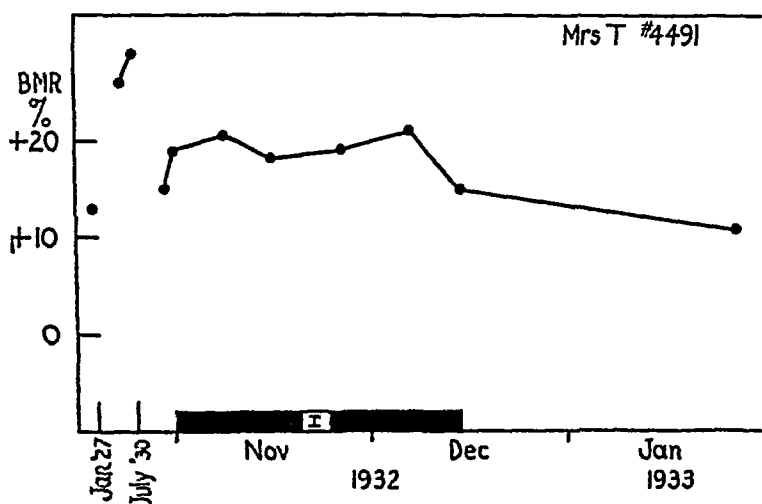


FIG. 5 Diagnostic test with iodine in the case of Mrs T Result negative

We did not see her again until this winter (1932-1933) She had had a baby between visits She claimed to be a bit nervous and to feel hot—nothing more There was a very questionable staring look of the eyes and a soft thyroid as before Very slight tremor was present—no other signs The basal metabolic rate was plus fifteen

We decided upon a diagnostic test with iodine because of the slight elevation of the rate The result is shown in the chart—a flat negative We believed this ruled thyrotoxicosis out Five weeks later the basal metabolic rate had dropped to plus eleven without further treatment and the symptoms were unchanged The original impression of colloid goiter thus proves to be correct The symptoms are not of thyroidal origin They require treatment directed toward the nervous system, not the thyroid

We have also considered to advantage a once shell-shocked veteran of thirty-six years who came to see us in our clinic in November 1931 He had had symptoms

of nervousness, exhaustion and trembling ever since the war. A goiter had been noted the year before. On physical examination we found moderate bilateral exophthalmos, stare and lid lag, and a slight, soft, symmetrical enlargement of the thyroid without bruit. His basal metabolic rate was plus twelve. We thought he had the remnant of a smouldering Graves' disease of long standing.

Followed over a period of three months without iodine the basal metabolic rate was found to fluctuate somewhat but showed no steady trend either up or down and did not average above the standard zone (Figure 6). Then on iodine for seven months it did the same. The chart shows not the slightest evidence of an iodine re-

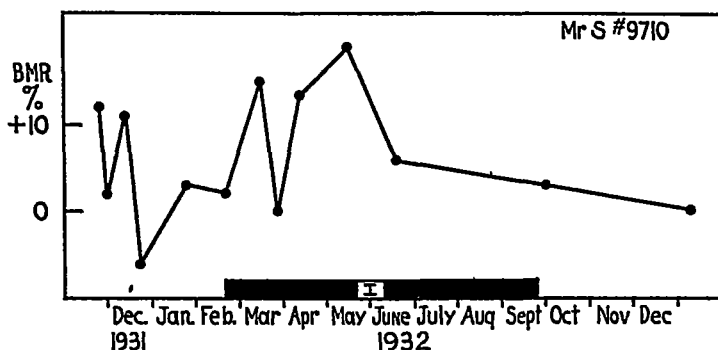


FIG 6 Diagnostic test with iodine in the case of Mr S. Result negative

sponse. He is exactly as well off without iodine as with it, both metabolically and symptomatically. He may have had exophthalmic goiter in the past and some exophthalmos remains but he is not thyrotoxic now. The problem for therapeutics is psychologic not endocrine.

Another case of considerable interest (Mr K) that has lately come to our attention is that of a business man of sixty-two who began to suffer from undoubted thyrotoxicosis at the beginning of last summer. His symptoms at the onset were subdued and on August 9, 1932 his basal metabolic rate was only plus sixteen. We had not control of his treatment and his own physician elected roentgen-ray treatment and iodine rather than operation which we would have advised. On this regime he improved, though on October 25, 1932 his basal metabolic rate was plus eighteen. During the course of the roentgen-ray treatment, although improving symptomatically in other ways, he developed exophthalmos which had not been present before. On January 14th, still on iodine, the course of roentgen-ray complete, he had a basal metabolic rate of minus twelve and felt well in every way except that his eyes were very irritated and becoming increasingly so. We omitted iodine and in eleven days the basal metabolic rate rose to plus five and symptoms of nervousness returned.

The situation was that the patient had been relieved of all symptoms except ocular ones on a regime of iodine and roentgen-ray. His basal metabolic rate was entirely within standard limits even off iodine. His goiter was very small and firm, his eyes were getting steadily worse. We were worried about his eyes. We believed that the rise in basal metabolic rate and increase in symptoms which took place when he was released from iodine control proved that an element of thyrotoxicosis still lurked, and we advised subtotal thyroidectomy in spite of his low metabolic rate, on account of his eye condition, although we would have been content to carry on with an expectant program had this not been present. I cannot tell you of the outcome for he is now undergoing preparation for operation.*

* Subtotal thyroidectomy was done on February 6, 1933. The gland removed showed hyperplasia typical of exophthalmic goiter. Iodine has been continued ever since, and the basal metabolic rate has dropped to a level in the neighborhood of minus twenty. In spite of this, the exophthalmos and ocular irritation persist and seem truly malignant.

I will present just one more case in which the test with iodine ruled thyrotoxicosis out. A married German machinist of forty was seen for the first time last September. His illness had covered eighteen months, the symptoms were excessive sweating, palpitation, precordial pain, dysphagia and nervousness. At the same time there had been progressive exophthalmos in the left eye. His right eye was of glass. His thyroid was small but palpable and rather firm. There was no thrill or bruit. He had a tremor of the fingers and fibrillary twitchings over his muscles, but no marked atrophy. The left eye though prominent showed no lid lag. His basal metabolic rate was plus nine. It was thought that exophthalmic goiter was probably present and he was admitted to the hospital. The next basal metabolic rate showed a rate of plus thirty-eight, but this was an isolated reading. The rest were between plus two and plus thirteen. On iodine there was no trend either up or down (Figure 7). It was concluded that he had no thyrotoxicosis and he was discharged.

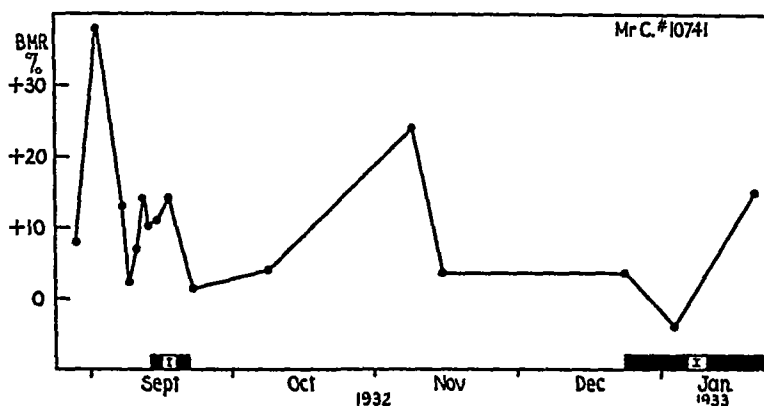


FIG 7 Diagnostic test with iodine in the case of Mr C. Result negative

Subsequent events have borne this out. There was one more isolated high reading but two others close to the zero line. A second trial with iodine showed no consistent change either way. Furthermore no improvement in symptoms when taking the drug was noted by him either time. This is as important as is the lack of change in metabolic rate. Truly thyrotoxic patients nearly always testify spontaneously to marked improvement while they are receiving iodine and to feeling worse when it is stopped. The cause of his exophthalmos remains in doubt. Of course he may return to us in the future with definite exophthalmic goiter but the test convinces us that he does not have it now.

In conclusion then I will repeat that in iodine we have an agent helpful in the diagnosis of thyrotoxicosis as well as in the treatment thereof. Whenever there is any doubt or question of its presence the effect of iodine should be observed. Isolated basal metabolic rates are not enough. Sufficient data to observe definite levels and trends must be obtained. The absolute level is of little significance. The fluctuation is what counts. A drop from plus nine to minus eight with iodine and return to plus nine when the drug is stopped is significant. When thyrotoxicosis is truly present, even though in slight degree, the response to iodine is definite, delicate and exact.

BIBLIOGRAPHY

1. V. C. F. H. The effect of iodine in exophthalmic goiter, *Ann. Int. Med.*, 1930, iv, 117-121.
2. V. C. F. H. Diagnosis and treatment of the several types of goiter, *Med. Clin. N. Am.*, 1931, vi, 791-792.

SCHIZOPHRENIA FROM THE PHYSIOLOGICAL POINT OF VIEW^{*}

By R G HOSKINS, PH D , M D , *Worcester, Massachusetts*

THE schizophrenic psychosis, of all unsolved problems, presents to the medical profession the outstanding challenge of our day. This disorder alone fills one-fifth of all hospital beds in the United States. It is presumably equally prevalent in other parts of the world. Its cost is incalculable. Its onset is commonly in the early years of maturity and it persists to a greater or lesser degree of severity throughout a lifetime that is not greatly curtailed. To the patient it represents exclusion from family and friends—literally in many cases, spiritually in any case. It casts a pall of undeserved stigma upon the entire family in which it strikes, and no family is exempt. There is probably no other disorder known to medicine that exacts so great a cost in prolonged unhappiness as does schizophrenia.

No more can the monetary cost be calculated. In our country approximately one hundred and fifty thousand able-bodied citizens are removed from productive pursuits to be maintained in special institutions. In Massachusetts the average period of hospitalization is about eleven years. In addition to the hospitalized population there are probably as many schizophrenics outside of institutions who contribute relatively little to society. At best they are inoffensive incompetents and at worst they constitute a portion of the criminally insane with hobos, prostitutes and other less offensively queer people falling in between.

Numerous items go to make up the toll of the social loss from the disorder. The hospital victims are expensive to maintain. In the United States the total investment in buildings for their care amounts to nearly a half billion dollars. Interest charges and depreciation on the buildings and their equipment are heavy and increasing items. In addition there are all the various maintenance costs—food, clothing, professional services, etc. The cost of the non-hospitalized group can only be guessed at but it must be a very considerable drain on families and on social agencies. From careful consideration of such cost items as are known and conservative estimate of others, the loss from this disorder appears to be in excess of a million dollars a day and estimates of twice that sum have been made.

Schizophrenia is as varied in its individual manifestations as is human nature itself. Under one name or another it has been known from the beginning of medical history. The schizophrenic picture can be recognized in the devil-possessed people of biblical and medieval times. The witchcraft delusion would seem to have amounted largely to a panic-stricken, confused recognition of the existence of schizophrenia. It remained, however, for Kraepelin only a generation ago to delimit the psychosis as an entity under

^{*} Read at the Montreal Meeting of the American College of Physicians, February 9, 1933

the designation of *dementia praecox*. Of late years Bleuler's term, *schizophrenia* (split mind) has largely come into use as more accurately descriptive of the disorder. Actually, the patient does not necessarily become demented nor does the disorder always show early onset, as Kraepelin's designation implies.

In modern psychiatric thought schizophrenia, or perhaps more accurately, the schizophrenic reaction, consists of two fundamental deviations from normality, together with an assortment of secondary features that give a kaleidoscope variety to the individual clinical pictures. Bleuler's primary characteristics are disorders of the association processes and a partial loss of contact with reality that is indicated in the term *schizophrenia* itself. Scarcely less characteristic are disturbances of the emotions. From the point of view of the physiologist, Kraepelin's definition of the psychosis as "a peculiar disorganization of the inward coherence of the psychic personality with predominating damage to the affective life and will" seems particularly suggestive.

The psychosis presents a bizarre *mélange* of psychologic normality and abnormality. Memory and orientation tend to be well preserved. The patients often show little disturbance of apprehension. Despite frequent appearances to the contrary, they are usually rather well aware of what goes on about them. Many pages would be required to present even an elementary account of the manifestations of the disorder. We may mention only hallucinations, delusions, poor judgment, incongruity of emotions—commonly with apparent neutrality or indifference—incoherence in train of thought and displacement of normal volitional responses by automatic or impulsive reactions. Bizarreness of conduct is seen in infinite variety.

Jung and numerous other writers have commented on the resemblance of the schizophrenic psychosis to the normal dream state. It differs from your dreams and mine mostly in that upon awakening from sleep the dream is not dismissed and in that the activities of the dream are largely carried out rather than merely visualized. The schizophrenic state and the dream state are strikingly similar in the free use of symbolism. Things do not mean what they seem but what they signify in the patient's own particular code. If the reader will imagine that he had been awakened from a vivid dream but that as he went about his daily affairs the dream continued to occupy the greater part of his attention, to dominate his thought and his activity, he will have a sufficiently accurate picture of schizophrenia for purposes of this discussion. Largely it is a manifestation of more or less disguised wishes or fears masquerading as accepted reality.

To one studying the phenomenology of schizophrenia from the physiological point of view the first question that presents itself is this: Could the manifestations of the disorder arise from organic causes or must we seek for some mysterious "dynamic" influence, an unresolved Oedipus complex or what not? Unquestionably earlier emotional experiences play an important role in the coloring of the individual picture, but are they necessarily connected in the genesis of the psychosis itself?

The answer would seem to be clearly in the negative. Point for point, the individual symptoms can be paralleled from conditions that are clearly organic in origin. In our dreams we are all rather schizophrenic, and perhaps no more mysterious etiology is involved here than depressed oxygen consumption in the brain cells. The victim of chronic alcoholic intoxication may show hallucinations and delusions quite as striking as those of the schizophrenic. The rich imagery of acute morphine intoxication and especially the hallucinations of mescal poisoning are phenomena of the schizophrenic order. Even the motor manifestations of catatonic dementia praecox can be closely simulated by the administration of bulbocapnin. In the perennial debate between the organicists and the psychogeneticists the fact is frequently overlooked that the individual symptomatology of schizophrenia can be duplicated in almost every particular by the manifestations of dementia paralytica. In this latter psychosis we seek for no more mysterious causation than the syphilitic organism. Were the fact not known that dementia paralytica is caused by syphilis the literature would no doubt be quite as full of "dynamic" analyses and speculations as is that devoted to schizophrenia, and we might still be seeking in them the primary cause of the disorder.

Schizophrenia, then, could be caused by strictly organic factors. As a matter of fact, does the evidence compel us to assume an essential organic element in the causation? The disorder shows a striking predilection for individuals of "tainted heredity" and those of dysplastic constitutional types. Our most instructive single datum is the comparative double incidence of schizophrenia in identical as compared with ordinary, fraternal twins. Unfortunately the data are not yet sufficiently numerous to be entirely compelling but so far as they go they indicate that if one of a pair of identical twins develops schizophrenia his fellow twin has relatively little hope of escaping, whereas if one of a pair of fraternal twins develops the disorder his fellow is in no special danger. Identical twins are organically two parts of the same individual, whereas fraternal twins are quite as dissimilar as are other children of the same family. Organically the two types of twins are entirely different but there is no reason to assume that the emotional experiences of the two sorts are particularly different. These three categories of facts seem to allow no escape from the conclusion that organic factors are important in the chain of causation whether or not they are invariably operative. This is true irrespective of what weight one may assign to psychogenic factors. Apparently, then, the individual develops schizophrenia primarily because he was born to have it. If this conception is true the most important question confronting the investigator is: What is organically peculiar about the schizophrenic?

During the past five years my collaborators and I at the Worcester State Hospital have been attempting to learn as precisely as may be the answer to this question. During this period some 300 cases have been rather elaborately studied, not only as regards their psychologic and psychiatric char-

acteristics but especially their physiologic. The outstanding result of the first four years' work was to demonstrate in the individual patient a remarkable degree of variability of the physiologic functions from one test to another. So troublesome had this feature of variability become that last year we decided to devote the entire resources of the research service to a study of the variability, as such. This engaged the entire time of some 50 or 60 people, including nurses and attendants, for about a year.

Each patient received a detailed physical examination to eliminate organic disease that might serve as an unnecessary complication of the problem. Any one showing other than minor passing ailments was rejected. A detailed social history was compiled for each patient. He was given an intensive psychiatric study to insure that he was actually suffering from schizophrenia. He was then subjected to seven months of intensive investigation following the schedule set forth in the accompanying table (Table 1). After a month of study by this schedule he had a two months'

TABLE I

Schedule

<i>First Week</i>			
<i>Monday</i>	9 00 a m	Psychometrics	1 00 p m Physical and psychiatric examinations
<i>Tuesday</i>	9 00 a m	Psychometrics	1 00 p m Physical and psychiatric examinations
<i>Wednesday</i>	9 00 a m	Psychometrics	1 00 p m Physical and psychiatric examinations
<i>Thursday</i>	7 30 a m	"Basal metabolism" including rectal temperature, pulse, blood pressure, weight, height. Blood samples collected for quantitative analysis and phytotoxic test	1 00 p m Psychiatric examination
	9 30 a m	Breakfast	
<i>Friday</i>	7 30 a m	"Basal metabolism"	1 00 p m Diagnosis by admitting staff Psychiatrist's note
	9 30 a m	Breakfast	
<i>Saturday</i>	7 30 a m	"Basal metabolism"	p m Mental note
<i>Second Week</i>			
<i>Sunday</i>	1 m	Rest	p m Rest
<i>Monday</i>	9 00 a m	Experimental psychology	1 00 p m Psychiatric ward observations
			3 00 p m Photography—2 nude poses
<i>Tuesday</i>	9 00 a m	Experimental psychology	1 00 p m Psychiatric ward observations
<i>Wednesday</i>	9 00 a m	Experimental psychology if not previously completed	1 00 p m Psychiatric ward observations
<i>Thursday</i>	8 00 a m	Oculo-cardiac test	1 00 p m Psychiatric ward observations
			1 30 p m Dental examination and x-ray studies of skull, chest, and gastrointestinal tract
	9 20 a m	Breakfast	
	10 00 a m	Blood volume, plasma volume, blood gases, blood pH, blood urea nitrogen, blood sugar, blood cholesterol, blood creatinine, blood urea, blood creatinine, blood urea, blood creatinine	3 00 p m Schuster Test of cardiovascular efficiency Psychiatric ward observations
			p m Rest

TABLE I—(Continued)

Thurd Week

<i>Sunday</i>	7 00 a m	Start 24-hour urine col-	p m	Urine collection
		lection		
<i>Monday</i>	7 00 a m	Finish urine collection	2 30 p m	Blood pressure
	8 30 a m	Inject phenolsulphone-		
		phthalein Collect specimens		
<i>Tuesday</i>	7 00 a m	Start collection of 24-hr	1 00 p m	Psychiatrist's note
		urine		
	7 30 a m	"Basal metabolism,"		
		"Lung volume"		
	9 30 a m	Breakfast		
<i>Wednesday</i>	7 00 a m	Complete 24-hr urine col-		
		lection		
	8 30 a m	Inject phenolsulphone-		
		phthalein, collect specimens		
<i>Thursday</i>	5 00 a m	Galactose tolerance con-	1 00 p m	Psychiatrist's note
		trol sample		
	6 30 a m	Collect samples for blood		
		chemistry and blood morphology		
	7 00 a m	Galactose tolerance test.		
<i>Friday</i>	5 00 a m.	Repeat galactose tolerance	1 00 p m	Psychiatrist's note
		test		
<i>Saturday</i>	5 00 a m	Repeat galactose tolerance	1 00 p m	Psychiatrist's note
		test		

Fourth Week

<i>Sunday</i>	a m	Rest	p m	Rest
<i>Monday</i>	8 00 a m	Fluoroscopic gastrointes-	p m	Gastrointestinal series
		tinal studies begun Psychiatrist's		
		note Internist's note on physical		
		status		
<i>Tuesday</i>	a m	Gastrointestinal studies contin-		
		ued Psychiatrist's note		
<i>Wednesday</i>		Gastrointestinal studies continued		
	8 00 a m	Blood sedimentation test		
		Bromsulphonephthalein test for liver		
		function Psychiatrist's note		
<i>Thursday</i>		Gastrointestinal studies continued	p m	Psychiatrist's note

rest period during which, however, certain accessory tests of the cerebrospinal fluid, of the reactions to various drugs that act on the autonomic nervous system, and of the liver functions were made. The studies of the main schedule were then repeated, another rest period was interposed and finally a third month of study was carried out. Many of the tests were made in duplicate and some in quadruplicate, hence at the end we had from three to twelve tests on each patient. Some 65 patients have now been through the entire series of tests but this report will be based largely on the tabulated results obtained in the first 54 patients of the series.

Suffice it to state that in many of his physiologic activities the schizophrenic is strictly normal, though perhaps unusually variable. Attention will be directed mostly to those features in which abnormality proved to be characteristic.

The Urine The urine was strikingly normal as regards total solids, total nitrogen, nitrogen partition and microscopic residue. Just as striking

was its abnormality as regards volume. The individual variability in this respect was high but the average volume for the series was about twice the normal amount. Table 2 sets forth the results that were obtained in 26

TABLE II
Urinary Volume

	Min	Max	Range	Mean	Stand Dev
Normal subjects (26)	655	2805	2150	1328 \pm 83	629 \pm 59
Schizophrenic subjects* (44)	510	8000	7490	2602 \pm 120	1851 \pm 85

* All catheterized

normal subjects as compared with those of 44 patients from whom the specimens were obtained by catheter. The most striking features of the table are that the average output of the patients was 2602 c c per day as compared with 1328 for the controls and that the variability was about three times as great. The total solids being normal and the volume high the specific gravity was of course correspondingly low. In individual cases we have often obtained volumes from three to eight liters per day. In 48 of the 63 patients studied to date the average volume was above the conventional high normal of 1500 c c. These findings were entirely unexpected and their significance is by no means clear. They suggest either a high incidence of disturbed function of the diencephalon or of the posterior lobe of the pituitary gland. They prove that in at least one respect the average schizophrenic patient is quite as abnormal physiologically as he is psychologically.

Blood Chemistry. The chemical constituents of the blood were also for the most part strictly normal on the average but they also showed a rather high variability. The blood cholesterol averaged slightly low as compared with findings in a control series of 24 subjects but the variability was so great as to cast some doubt upon the validity of the difference. The blood gases and blood pH were normal on the average and showed about a normal range of values with the exception of the venous oxygen which in individual cases was strikingly low.

Blood Morphology. The various blood counts were found to show a normal range in most respects, but a slight secondary anemia ran through the picture, being seen in fairly well marked degree in more than half the cases. The average red cell count was 4,957,000 which, for adult males, is slightly low. The total white cell count, as many other observers have noted, was somewhat high, the average being 10,477. The variability from patient to patient and in the same patient from period to period was notably great.

Gastrointestinal Motor Functions. The motor functions of the upper gastrointestinal tract were quite normal as determined by roentgen-ray studies following barium meals. In the colon, however, considerable stasis appeared to be characteristic, the average emptying time being 74 hours.

Carbohydrate Metabolism. The fasting blood sugar was strictly normal in its average namely, 60 mg per 100 c c, and in its range. We

have not studied the reaction following ingestion of glucose or the injection of adrenine but the evidence in the literature indicates a frequent prolongation of the hyperglycemic curve. We used as an index of the carbohydrate metabolism the galactose tolerance as recommended by Rowe. This was found to be highly variable in the individual patients but the average was 22 grams as compared with Rowe's average of 30.

The Liver Function There are many features in the schizophrenic psychosis that suggest the operation of a toxic factor. One of the obvious sources of obscure metabolic intoxication is the liver. We have attempted to test the functional integrity of this organ in a variety of aspects as brought out by nearly all of the standard liver-function tests. The voluminous details are difficult to epitomize. Suffice it to state that the general trend of the evidence indicates that the liver in one or other of its functions is abnormal in a fairly high proportion of our cases. And this despite the fact that our series included a considerable number of chronic as contrasted with acute cases in which, according to other investigators, incidence of liver dysfunction is especially high.

Phytotoxic Reaction Macht, following several earlier investigators, has described a method for the detection of metabolic toxins by use of seedlings of the plant *Lupinus albus*. Looney and Macht were able to show that the blood of patients presenting marked depression is definitely toxic to these seedlings, just as Macht reported the blood of menstruating women to be. We had hoped by this technic to discover some evidence of the long-sought schizophrenic toxin, but the results were negative. If the schizophrenic is characteristically a victim of metabolic intoxication the toxin either works so slowly and at such low concentration as not significantly to affect the growth of *Lupinus albus* or else it is of a nature to which this plant is immune. Parenthetically, in view of the emphasis that Holmes and others have placed upon colonic "auto-intoxication" as a cause of schizophrenia it is interesting to note in passing that our patients, despite a high incidence of stagnation in the lower bowel, have seldom showed indicanuria.

Respiratory Complex Perhaps the most striking abnormality in the metabolic picture of schizophrenia as we have seen it is in the composite group of findings relating to respiration, in the broad sense. The patients as a group showed a characteristic hypometabolism. The basal blood pressure averaged about 100, the basal pulse rate, 59, and the average oxygen consumption rate, 89 per cent of standard normal. The average weight was found to be 62.6 kg. which for the age and height was about 16 per cent below prediction. By way of illustration, in table 3 are presented the chief elements in the respiratory complex of an individual subject as determined on 12 different occasions over the course of seven months. The clinical condition of the patient showed relatively little variation within this time, hence the findings need not be discounted as mirroring a fluctuating psychosis. The data are more than commonly satisfactory, too, in that the patient was in good nutrition throughout the period of study.

TABLE III
Respiratory Complex

	First Period	Second Period	Third Period
	8/18/31	11/29/31	11/10/31
ht	73 0 kg	73 6 kg	74 0 kg
vol (spirometer), % of normal	94	50	60
tional index, % of prediction from			
ght-age	100	101	102
	8/5/31	10/29/31	1/21/32
en consumption, % of prediction	97	71	66
l pressure, mm Hg	96/58	104/70	110/56
	48-50	44-44	36-42
erature, rectal	99 2	98 2	98 8
ratory rate	14-15-14	15-15-14	13-14-14-14
	8/6/31	10/30/31	1/22/32 *
en consumption, % of prediction	89	76	77
l pressure, mm Hg	122/78	96/60	98/52
	54-52	44-42	34-38
erature, rectal	99 4	98 4	99 0
ratory rate	16-17-16	14-14-13	16-15-16
	8/7/31	10/31/31	1/23/32
en consumption, % of prediction	100	72	69
l pressure, mm Hg	116/68	94/50	98/56
	54-54	40-40	33-35
erature, rectal	99 2	98 0	98 8
ratory rate	20-20-20	12-13-13	12-13-13
	8/18/31	11/10/31	2/2/32 *
en consumption, % of prediction	81	76	71
d pressure, mm Hg	108/80	94/48	110/66
	44-46	50-50	44-48
erature, rectal	98 2	99 0	98 8
ratory rate	20-24-24	12-14-16-15	10-10-11-12

* Oxygen consumption rate 1/22/32—77%. During this test workmen overhead were making a great deal of noise. The patient was restless, wandering about the room before he could be persuaded to lie down. He said he did not want to take the test. Oxygen consumption rate 2/2/32—71%. A great deal of hammering overhead, continuous and disturbing but apparently calm, however.

With the exception of two occasions on which workmen were making considerable noise overhead the determinations were all made under technically satisfactory conditions. The patient had been brought to the laboratory before breakfast and had lain quietly for a half hour before the observations were made. The table is mostly self-explanatory. Suffice it to state that the oxygen consumption rate is expressed in terms of percentage of normal prediction, the findings being calculated to both the DuBois and Harris-Benedict standards and the average taken. Special care was observed to prevent leakage from or into the system and the use of spent soda lime was rigorously excluded by test of the reagent. Such errors as exist in the determination therefore were necessarily in the upward direction. Accordingly, if as was usually the case, the two determinations were routinely made at each session differed from each other, the lower was selected as most nearly approximating the basal. It is probable, however, that the rate even so selected was substantially higher than the true basal.

For an earlier paper on this subject see the following article: Hoskins, R. G., "Oxygen consumption ('basal metabolic rate') in schizophrenia," *Arch. Gen. Psychiatry*, 1932, 1, 136-145.

It will be noted first of all that the rate of oxygen consumption was strikingly variable as between the first and the other two periods and to a considerable extent within the given periods. In the first period the range was from 81 to 100 per cent of normal and in the third from 66 to 77 per cent. The nutritional level was the same in the first and second periods but there was a falling off from 101 to 94 per cent of the normal weight between the second and third periods. The blood pressure was even more variable, ranging from 94/48 to 122/78 in the various cases. It must be emphasized that the patient was lying quietly in each case with no detectable evidence of tension. The pulse under similar conditions varied from 33 to 54 beats per minute. The temperature also was slightly subnormal though not strikingly so.

The oxygen consumption rate, then, is characterized by a high degree of variability as are the associated findings. The only probable source of error in the blood pressure determination is concealed psychomotor tension of the subject. We are disposed therefore to regard the lower values, namely 94 to 98, as most representative of the true characteristic basal level.

The data would bear further discussion from several points of view but suffice it to state that the patient conformed to the trend of the entire series in showing low blood pressure, slow pulse and reduced oxygen consumption rate—all of which would be conducive to reduced level of activity of the brain cells and all of which are, as a matter of fact, conditions that are characteristic of ordinary sleep.

Emphasis must be laid on the fact, however, that the patients, although basically in a metabolically somnolent condition, retain the ability under stimulation to arouse at least temporarily to a more normal condition. Thus the same patient who was shown to have a basal blood pressure of less than 100 was found when subjected to special efficiency tests in the afternoon to show a level ranging from 115 to 132 mm.

But the approach to normality in the average case is only partial. In 200 determinations of blood pressure and pulse rates made on our patients in the mid-afternoon these features averaged significantly low as compared with those obtained by Schneider under similar conditions in 2000 tests on aviators. The differences are shown in table 4. Under moderate exercise

TABLE IV

Averages of Pulse Rate and Blood Pressure in Schizophrenic as Compared with Normal Subjects

	200 Tests on Schizophrenics	2000 Tests on Aviators
<i>Reclining</i>		
Pulse rate	64	74
Systolic blood pressure	112	118
<i>Standing</i>		
Pulse rate	81	91
Systolic blood pressure	119	120

(Courtesy of Dr J M Linton)

the blood pressures of the two groups equalize but the pulse rates of the schizophrenics continue to lag

The schizophrenic differs in his respiratory metabolism from the normal person in another important respect One of the striking adaptive mechanisms of which we all make greater or less use in avoiding obesity is the stimulating effect of food, and especially protein food The more protein we eat the more fuel we burn In the schizophrenic subject this is not so, according to statistical tests The protein food metabolised is mirrored in the total nitrogen excreted in the urine In normal subjects according to an analysis made by E M Jellinek of our Staff, there is a definite positive correlation between the total urinary nitrogen and the oxygen consumption rate In schizophrenic subjects the correlation is practically nil This fact would seem to indicate that the schizophrenic fails to get the stimulation from protein consumption that the ordinary person experiences

The characteristic variability of the test findings was partially illustrated in table 3 The range of some of the other findings in the same patient is shown in table 5 The table sufficiently indicates the futility of attempting

TABLE V
Extreme Values Noted in an Individual Case

Oxygen consumption rate	100 %	66 %
Blood pressure—systolic	122 mm	94 mm
Pulse	54	34
Temperature (rectal)	99.2°	96.6°
Urine volume	1960 c c	510 c c
Galactose tolerance	40 gm	20 gm
Erythrocytes	4,160,000	4,630,000
Leukocytes	15,200	10,300
Lymphocytes	42 %	18 %
Blood non-protein-nitrogen	49 mg	32 mg
Blood sugar	116 mg	88 mg
Colon emptying time	168	96

to appraise the physiological status of a schizophrenic subject from single tests As a matter of random chance the values obtained in any one examination might have fallen anywhere between the extremes noted If more tests had been made in the case cited the range would probably have been still further extended

According to our findings, then, the schizophrenic patient is quite as abnormal physiologically as he is psychologically First of all, he is a very unstable person In Cannon's parlance, his *homeostasis*, i.e., his ability to maintain a metabolic "steady state" is defective In numerous respects the fluctuations center about normal levels but in other respects the basal levels are disturbed Apparently most fundamentally significant is the reduction in the activities having to do with body oxidation—the circulatory system and the specific dynamic action of protein The similarity of the metabolism of the resting but well-fed schizophrenic with that of the normal person is striking Perhaps the characterization of the psychosis as

a dream state is worthy of more literal acceptance than had previously been supposed. A dreaming mind in a somnolent body appears to be the fundamental condition of the psychosis. The body, however, is rather easily aroused whereas the dream state is notably resistant to correction.

In addition to the hypometabolism, the increase in urine volume seems equally characteristic.

Which is cause and which effect? Does the psychosis cause the physiologic abnormalities or does it result from them? Or are all the recognized abnormalities joint results of some more fundamental defect? Such data as those reported fail to determine the question. The researches herein reviewed are strictly at the descriptive level and at this level causation does not emerge. The data have as their chief significance the setting of a problem for more penetrating research. Some of the specific individual questions that are raised we now have under study.

Humanity has much at stake in such researches. Many attempts have been made to find a successful cure for schizophrenia. Numerous ways of palliating the disorder are known but nothing genuinely curative. By all the teachings of medical history essentially the only hope is first to discover the cause. Then and then only can intelligent efforts at cure be devised. Only the most improbable fortunate accident will bring us sooner to the goal.

Of the millions of dollars now being expended annually for medical research on this continent, how much is being devoted to this, the greatest problem of all? One per cent would be an extravagant estimate. Compelling statistics are not available but some idea of the neglect of the problem can be obtained by noting the relative numbers of articles appearing in medical journals. In the Quarterly Cumulative Index Medicus for 1931 there are listed many thousands of articles on human diseases. Of the various disorders the list of articles on tuberculosis ran to 620 column inches, the stomach and its diseases, 214 inches, the thyroid and its diseases, 137 inches, cancer, 190 inches, while schizophrenia bulked a mere 39 inches. Perhaps the measure of our own culpability is better indicated by the fact that from all the periodical publications on the North American Continent in this same year, 1931, there were listed but 26 articles on dementia praecox in any of its aspects. And that psychosis fills one-fifth of all hospital beds.

Those stark facts speak for themselves. Medicine has put society in its debt in innumerable ways but until the researches in schizophrenia are multiplied manyfold its whole duty will not have been done. The problem is admittedly difficult but clues for its solution are available. For all that any one knows to the contrary schizophrenia may be entirely preventable or curable. To go on suffering its ravages without making a much more respectable effort than has yet been made in our own defence would seem to amount to sheer social stupidity.

SUMMARY

A brief report is offered of the results of a five-year cooperative research program at the Worcester State Hospital on the psychosis, schizophrenia

The disorder was found to be characterized physiologically by two sorts of deviation from normality. In numerous respects the individual patients showed marked variability from one functional test to another but in most regards the average functional level was found to be essentially normal. The average urine volume, however, was about twice that of non-psychotic subjects living in the same environment. There was a tendency to secondary anemia and moderate leukocytosis was common. The galactose tolerance averaged 22 grams as compared with a reported normal average of 30 grams. The motor functions of the colon were retarded. The complex of functions centering about oxygen metabolism was found to be characteristically abnormal. The blood pressure, pulse rate and stimulating effect of protein were reduced as was the actual oxygen consumption itself. As a group the patients were moderately underweight despite generous dietaries. Further studies as to how these abnormalities are brought about might throw significant light on the cause of the psychosis. There are suggestions that pituitary deficiency may play an important rôle.

Emphasis is laid on the fact that schizophrenia presents the outstanding medical problem of our time. It fills one-fifth of all hospital beds in the United States, its cost in money is great and in human suffering is incalculable. Practical clues are available for further study of the problem but it is receiving an almost negligible proportion of the total funds and efforts now being devoted to medical research.

EVALUATION OF THERAPY IN CHRONIC ATROPHIC ARTHRITIS*

By W PAUL HOLBROOK, M D , F A C P , *Tucson, Arizona*

THE treatment of chronic arthritis is still passing through a phase of promiscuous therapy, much as tuberculosis did 20 years ago. There has been a tremendous increase in interest concerning rheumatic diseases during the past ten years, and, as a result, the medical literature has been flooded with reports of cures accomplished by all conceivable types of treatment. As a consequence, the majority of clinicians have been unable to separate fact from fancy. Diets, vaccines, colonic irrigations, various forms of electro-, physio-, and hydrotherapy, typhoid vaccine injections, the administration of scores of chemicals orally or by injections, endocrine therapy, postural correction, and even the manipulation of the feet, have all been hailed by the public, and too often by the medical press, as the answer to the problem of treating chronic arthritis. It is most unfortunate that many of these methods have been made available to the general profession, for some of them are not only worthless, but are instruments of incalculable harm. The many remedies offered are of course the best evidence of a lack of specificity.

In an attempt to evaluate the many therapeutic procedures, the last 1000 cases of chronic arthritis passing through the hospital and clinic of the Desert Sanatorium have been grouped according to the different types of therapy employed and have then been carefully analyzed with regard to response. The classification of chronic arthritis has been discussed in detail in previous papers. A brief outline of classification, given in table 1, will serve to identify the type under discussion.

I *Atrophic Arthritis* In our experience atrophic arthritis can be sepa-

TABLE I
Chronic Arthritis

- I Atrophic (Rheumatoid, Chronic Infectious)
 - a Without clinical evidence of infection
 - b With clinical evidence of infection
- II Hypertrophic
 - a Generalized of old age
 - b Localized, the result of injury or trauma
- III Spondylitis
 - a Without bony ankylosis
 - b With bony ankylosis
- IV Rheumatoid Affections
 - Myositis, fibrositis, neuritis

* Read at the Montreal Meeting of the American College of Physicians, February 10 1933
From the Desert Sanatorium and Institute of Research, Tucson, Arizona

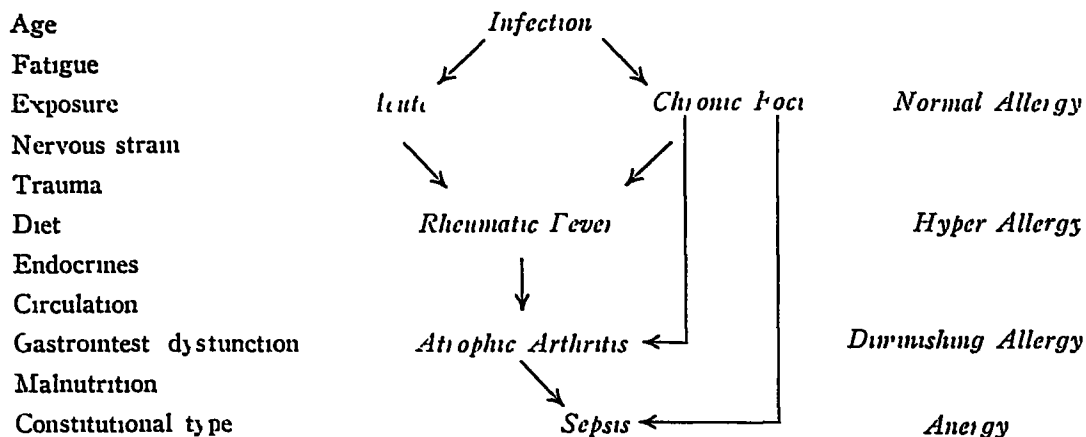
rated clinically into two general groups. The first, "a," is an atebri^{or}sidious, progressive, symmetrical, deforming, and crippling disease which occurs most frequently in women beyond the fourth decade. It is differentiated from the second group by its symmetry, the lack of fever, the early and marked widespread demineralization, the early cartilage destruction, the trophic skin and muscle changes, and the complete failure of therapy when directed toward infection or when the problem is attacked from the standpoint of foci of infection. It is a disease often dramatically affected by the patient's emotional life and is, in many instances, related to some form of gastrointestinal dysfunction. The second group, "b," is characteristically what is known as chronic infectious arthritis. There is, however, in contrast to group "a," fever, malaise, red or hot joints, and other constitutional symptoms of infection. In its most acute phase it may resemble rheumatic fever. It should be understood that the separation of atrophic arthritis into two groups is made solely on a clinical basis and especially because of the difference in response to treatment. These groups may possibly represent only a different response to common etiological factors.

Inasmuch as chronic atrophic arthritis constitutes the real stumbling block in therapy, and because of space limitation, our discussion will be confined wholly to this group, of which there are more than 300 in this series. In reporting results from treatment, only generalizations will be offered. The reporting of results in percentages cured and improved, through the employment of a certain therapeutic procedure, has always been a source of amazement to us. Everyone who deals with such patients over long periods of time realizes that such statistics are almost entirely dependent upon the statistician. These patients in our series have been followed closely and at frequent intervals checked with regard to joint swelling and mobility, blood pressure, distribution of bone minerals, temperature range, blood count, sedimentation time of erythrocytes, pain, and general symptomatology. These were the criteria used in estimating improvement.

Our concept of chronic atrophic arthritis does not admit a known single specific etiological agent, nor likewise a specific cure. There are many factors concerned in the etiology of this disease, and it is a disease not only of the joints but is constitutional in scope, manifesting itself in nearly every system of the body. The following diagram (table 2) schematically illustrates this.

This illustration is intended to show the complexity of etiological factors and the difficulty of a direct approach to therapy. It is possible, at a glance, to see the enormous number of combinations available with so many variables. The manifestations of infection are in a large measure determined by variations in other factors, a few of which are listed in the first and third columns. We do not know that infection always begins with the factors, though there is considerable evidence to suggest it, but the diagram is an illustration of the possibilities. When one considers this complexity of the etiology of therapy, it becomes exceedingly complicated.

TABLE II



and illustrates well the fallacy of assuming that certain results in treatment are due to one specific therapeutic agent. It is because of the many sided nature of such a chronic disease that therapy, to be effective, must depend not upon one agent but upon every factor possible. Therapy then, of chronic atrophic arthritis, should concern itself first of all with the patient's general health and it is with this in mind that, after trying a long list of therapeutic measures, we have selected but a few that seem worthy of mention. These are tabulated in table 3.

TABLE III

General Therapeutic Measures

Rest and Exercise
Heat and Massage
Prevention and Correction of Deformity
Diet
Bowel Management

Special

Removal of Foci
Transfusion
Vaccine
Climatic Therapy
1—General—Residence
2—Special—Heliotherapy

All of these patients with atrophic arthritis received the first five general measures, as well as general climatic therapy. In addition to these measures, approximately 100 patients had foci of infection removed, 70 were transfused, 100 were given vaccine, and 100 had only special climatic therapy in addition to general measures. Every attempt was made to establish an adequate control period on general measures, before beginning any one of the special types of management.

GENERAL MEASURES

Rest and Exercise One of the first problems confronting the physician is determining the relative proportion of rest and exercise desirable for a given patient. In general, rest should be directly proportional to the acuteness, and inversely proportional to the imminence of ankylosis. Exercise should almost always be active and almost never passive. Motion should be limited to within the painless arc, but pushed to the limit with some assistance. All exercises should be done slowly and exactly, with a rest interval

before the next one is begun. We use under water exercises in much the same way as they are used at Warm Springs, Georgia, for paralytics. A very much wider range of joint motion can be secured without pain or muscle spasm than is otherwise possible. By varying the temperature of the water, any degree of sedative action or of stimulation can be secured. We are firmly convinced that the salvation of many patients with chronic arthritis depends upon regular and wisely directed exercise, for with atrophic arthritis in its more chronic phases, it is truly a case of use or lose.

Heat and Massage The application of local heat to the joints is, in our opinion, utilized too much and is a factor in keeping an arthritis active that might otherwise subside. The greatest precaution should be exercised in utilizing heat, unless the stage of the disease is a very chronic one. Diathermy, as a method of heat in these atrophic demineralized joints, has in many instances precipitated exacerbations and has produced further demineralization. Massage, in the acute stages, should be avoided, and only with increasing chronicity should stimulating massage be used. Light massage can be used very early and is the best substitute if active motion is not possible. It is in other types of arthritis that heat and massage are indispensable. It should be noted that the "a" group tolerate heat and massage much better than the "b" group. Local heat to the joint ought not to be followed at once by exercise, as is generally done. Stripping, depletion massage, or rest should precede exercise as further damage will occur in exercising an engorged joint. Massage and active educational exercises provide three-fourths of the physiotherapy given in our Hospital. It should be pointed out that little special equipment is necessary for this work, but a trained personnel is essential.

Prevention and Correction of Deformity In every case of atrophic arthritis, the possibility of residual deformity in any and all involved joints should be anticipated. The prevention of such deformities can be accomplished only at the price of eternal vigilance. Their correction requires infinite patience. Nearly all deformities in this unhappy disease occur in flexion. Particularly is this true of the spine, elbows, wrists, hips, and knees. Eighty per cent of all patients with chronic atrophic arthritis, entering our clinic, have a flexion deformity of one or more joints, which might have been prevented. In the acute stage the joints should be at rest at the normal angle of relaxation. Light splints, or light weight plaster of paris shells, are most useful in maintaining the ideal position of the joint. Weight bearing upon a bent knee is not only painful, but increases the deformity. Flexion deformity of the knee can usually be prevented by the simple use of a posterior splint, and a knee already so deformed can in most instances be straightened by the application of a series of plaster of paris posterior casts. Painful pressure, wedge casts, and calipers are not usually necessary, and relaxation and protection will usually bring the knee to a normal weight bearing angle. Corrective exercises accompanied by proper rest are necessary. Group muscle exercises, particularly of the extensors, can be done

without joint motion and should be carried out routinely. Active joint motion, without weight bearing, can be begun very early and will maintain muscle tone and joint mobility without injury.

The feet and the proper fitting of shoes are of first importance, as the patient's ability to walk depends upon his feet. We are convinced that many patients, who might otherwise be reasonably free from discomfort, continue to experience the greatest difficulty in walking, because of improper shoes. It should be emphasized again that prevention of most deformities is not difficult, but correction is most painful and trying.

Diet Diet does play a very real rôle in the treatment of these patients. Dr. Pemberton of Philadelphia has said many times all that can be said on this subject, and with him we are in hearty agreement. A diet low in concentrated carbohydrates and high in vitamins is essential, where the patient's state of nutrition will tolerate it. A rigid dietary restriction we believe to be much more efficacious in the "a" group of atrophic arthritis than in the "b" group. Where the patient is poorly nourished and emaciated, we discard most dietary restrictions until a better state of nutrition is secured.

Bowel Management The majority of patients with atrophic arthritis have a history of gastrointestinal disturbances and, in most instances, complain of constipation. The colon is often tortuous, the sigmoid redundant, and there are areas of spasm in an otherwise very atonic bowel. Routine proctoscopic and sigmoidoscopic examinations, with cultures from the mucosa, have been made in more than 200 of these patients. The majority show some deviation from normal in the mucous membranes. Proctoscopic examinations have been repeated after a series of colonic irrigations, oil enemas, acidophilus implantations, etc., without noticing, except in a few instances, any demonstrable change in the mucosa. There is no doubt but that in our experience adequate bowel elimination has contributed to the patient's comfort and that joint exacerbations do occur in a number of patients when gastrointestinal disturbances occur. Adequate intake of vitamins is helpful, but we have been unable to demonstrate with any regularity the remarkable changes in the colon on this routine reported by other investigators. The stool reaction of these patients is nearly always alkaline. Normal stools are neutral or slightly acid. The colon bacillus grown at the pH of a normal stool is non-pathogenic for animals. The same organisms grown in an alkaline medium become highly virulent for animals. We have had considerable success in a small group of patients by maintaining a slightly acid reaction of the stool. Further work is being done in this field. Bowel regulation is ordinarily maintained without cathartics by the use of a good mineral oil, or mineral oil and agar by mouth. A small retention oil enema may be used at night if necessary. It is difficult properly to evaluate therapy, but a sufficient number of patients have been seen who present demonstrable changes in the joints with faulty bowel management to convince us that it does play a rôle in some patients.

We
ic arthr

SPECIAL MEASURES

Three hundred and seventy patients with chronic atrophic arthritis, after receiving the above general measures during a control period, were divided into four comparable groups. Each group was then treated by one of the four special therapeutic measures.

Removal of Foci of Infection (One hundred patients) The removal of foci of infection in the "a" group of atrophic arthritis (table 1), has been very disappointing. No single patient that we have seen in this group has unquestionably benefited by the removal of a focus. Quite the reverse is true, however, in the "b" group, where removal of foci early will many times abruptly halt the disease. Here again, however, the possibility of benefit by removal of foci decreases with the duration of the disease. This is indeed so striking that very rarely are we hopeful of a beneficial result from removing a focus, when the disease has existed as a full blown atrophic arthritis for five years or more. It is worthy of emphasis that in nearly all patients of the "a" group and most of the "b" group, who are in the very chronic stage, the removal of a focus is apt to be not only not beneficial, but to be followed many times by acute exacerbations. We have in the records of these patients many such instances when removal of foci was followed by an unmistakable increase in the severity of the disease. In the early stages of the "b" group, where striking benefit is most likely to occur, a real hazard still exists in the removal of foci. We not infrequently precede the removal of a tooth or tonsils in an ideal case with a transfusion and take particular care not to remove the focus during, or near, an acute phase of the disease. Patients in the early stages of infectious arthritis should be treated for a reasonable time by all other measures possible, in an attempt to arrest the disease, and then under the most suitable conditions removal of foci of infection should be accomplished. If foci are removed in the more chronic cases, it should be done because of general considerations and not with the hope of cure.

Transfusions (Seventy patients) Patients in the subacute and early chronic phases of infectious arthritis, with or without anemia, respond well and in not a few instances dramatically to a series of small blood transfusions. In the patient who responds well, the temperature drops to normal, the pulse rate is slowed, joint effusions disappear, and the patient goes on to gradual recovery. Transfusion, in our opinion, can be used with advantage routinely, in suitable cases, as it is one other aid that hastens recovery and prevents the disease from progressing to its more chronic aspects. Transfusion has been of little help in the very chronic afebrile patients, with far advanced bone changes.

Vaccines (One hundred patients) So voluminous has been the literature recently regarding the use of vaccine, and so much has been claimed for the various different kinds of vaccine, that we have attempted to carry out a study of vaccination in its use. We have given vaccines to com-

parable groups of patients, using a wide variety of antigens. Skin tests were made with autogenous cultures, as well as with stock arthritis-producing streptococci. Several strains of streptococci from other investigators were also used. Specific agglutinations with the patient's serum were done against these organisms. Stock or autogenous vaccine was given intravenously or subcutaneously in small doses and in large enough doses to produce slight reaction. Some patients were given only skin reacting organisms, while others were given only nonreacting ones. Still others were treated only with those organisms showing a positive agglutination. In general, almost every combination of antigen and method of administration has been tried on nearly every degree of atrophic arthritis. The results have been checked by repeating the skin and agglutination tests at intervals, as well as by clinical criteria.

Undoubted clinical improvement, not easily accounted for otherwise, occurred only occasionally. No single one of the above groups did well enough to show clearly superiority of results over other groups not receiving vaccine. Our best results with vaccines have occurred where an autogenous organism, which showed a strong positive skin sensitivity test, was used in small desensitizing doses intravenously. We have had a few dramatic results in this group of patients. The use of vaccine is not without hazard, as we see daily in the clinic patients who have had very unhappy reactions from its use. We have had an occasional unfortunate result in our own practice, in spite of exercising the greatest care. No patient offers a more difficult therapeutic problem than one who has had unfortunate vaccine reactions or one who has been highly sensitized by its use. Shock therapy, either by vaccine or nonspecific protein, is a hazardous procedure in patients with early or subacute forms of atrophic arthritis.

It is time to call a halt on the promiscuous injection of vaccines. There are investigators who report a large percentage of cures by giving millions of organisms intravenously. Others, equally sincere, report similar results when the equivalent of less than one organism is used. There are ardent advocates of subcutaneous and of the intravenous method of inoculation. Stock vaccines are championed by some and decried by others. Agglutination, complement fixation and skin reactivity have all been defined as guides to diagnosis and therapy. Constitutional reactions are believed to be desirable or harmful, depending upon the investigator. When the patient improves, the agglutination titer is thought to go very high or very low, depending upon the laboratory in which it is done. What then is the explanation for the many reports of cures secured by such diverse methods? There are two factors that may be responsible. The natural course of atrophic arthritis consists of cycles of exacerbations and remissions. Out of this group of patients 60 per cent recovered or were remarkably improved, from the first attack of the disease. Whatever form of therapy was being used at the time was naturally credited with the cure. We wish to emphasize again that particularly in the early stages of atrophic arthritis the

tendency is to remission, and that in this respect the course of this form of arthritis is not unlike that of pernicious anemia. Unfortunately, when the patient's arthritis recurs, he often seeks other medical advice, so that little is learned concerning the progress of the disease over a number of years. Successive exacerbations become more chronic in nature and less apt to be followed by a spontaneous remission. A second possible explanation is that the term "atrophic arthritis" is used very loosely and in many instances is incorrectly applied to patients with everything from pes planus to wry neck. It is also necessary to point out again that the state of the patient, classified by the investigator as "improved," is unsuitable for statistical data.

Clinical experiments are still in progress, but in our present state of knowledge we feel that vaccine has a limited value, is not a panacea, and should only be used as an adjunct in treatment and then only where complete facilities are available for following the patient and under experienced medical direction.

Climatic Therapy (One hundred patients) There are many difficulties encountered when one attempts to prove the specific effect of any therapeutic aid in chronic diseases, but this is especially true where climate is concerned. The resort to climatic therapy usually involves a change of location, which may provide a variation in daily routine, increased rest, freedom from annoying business worries, escape from unhappy domestic situations, and a psychic stimulation provided by a suggested new cure. All of these must be weighed and considered when discussing results. There are often in addition certain changes in diet, medication, bowel management, and activity, associated with the change of physicians. These many possible variables emphasize the necessity for the greatest conservatism when reporting results from a change in climate. There are, however, a number of significant observations that appear even under the strictest scrutiny to support the widespread belief that climate may be a predominant factor in the etiology and in the treatment of chronic arthritis. Several of these observations will be discussed briefly.

Some months ago, it occurred to this writer that climate might best be studied if comparable groups of non-nomadic people living under different climatic conditions could be investigated. Arrangements were made for a survey on a tribe of Indians who have lived continuously on the Tucson desert for several hundred years. The incidence of atrophic arthritis in these Indians could then be compared with that of Indians in other climates. This survey is still in progress but no cases of atrophic arthritis have been seen yet among these 5000 Indians. So far we have not examined the Indians in Montana, Wyoming or Dakota, but have reports that arthritis, acute and chronic, ranks high as a cause of disability among them. This is especially true of the desert Indians is more startling when one finds them eating a diet of beans and corn, and carrying about abscessed teeth and infected wounds of infection. No striking difference is found in the diet of the Indians in the two groups of Indians. There seems to be only a difference in climate.

One hundred and twenty-two physicians of this locality were written to, or interviewed, regarding the incidence of atrophic arthritis in native residents of this vicinity. There were but two cases reported. We have seen only one case of atrophic chronic arthritis in a resident in the course of this last 1000 patients.

It is also of interest in this connection to note that rheumatic fever is very rare in this locality and to report that of 52 patients referred to us in the past three years, with recurrent rheumatic fever, no patient has had a frank recrudescence during his stay here. Eight were in an acutely active phase on arrival, which subsided within a few weeks. One died in an acute phase shortly after arrival. It is of course recognized that sufficient activity may be present to produce rheumatic lesions but remain undetected clinically. We have used the clinical course, temperature range, electrocardiogram, and sedimentation time of erythrocytes as guides to activity. Coburn, in his recent book "The Factor of Infection in the Rheumatic State," makes out a very strong case for the beneficial effects of climate in rheumatic fever. His results in transferring patients with rheumatic fever to Puerto Rico are entirely in accord with our experience when such patients are brought to southern Arizona.

One hundred patients with atrophic arthritis were selected for this study on climatic therapy. They were selected without reference to severity of disease, but on the basis of having been treated as nearly as possible by general and special climatic modalities alone. No patient was included who had foci of infection removed, or who was treated with various specific medications or vaccines. Patients who had special diets and exercises could not be excluded, and there were without doubt many other uncontrolled factors. It is only fair to state that a large majority of our patients come to us in a very chronic stage of the disease and may be termed "last resorters." The results in this group of patients have been most gratifying. The majority have made definite and sustained improvement. A few made dramatic recoveries, and a few were unable to accomplish any distinct gain at all. As has been stated before, the number of variable factors is so great that no proof can be offered as to the specific rôle played by climate in this group of patients. It is equally difficult to evaluate any other type of therapy. We were, however, convinced by comparing their previous experiences with various types of treatment, that climate played a very important rôle in the improvement secured.

The total effect of climate is a composite of such things as humidity, temperature range, altitude, barometric pressure, wind velocity, rainfall, concentration of ultra-violet, total sun energy, ionization of air, type and character of exposure to sun, etc. We are now attempting to determine which are the significant factors. Graphic records are being kept on all of the above data and these are being studied in conjunction with the patient's signs and symptomatology. A warm, dry climate and a minimal barometric variation at present seem essential. Various forms of heliotherapy constitute the major portion of specific climatic therapy.

It is not the intention of this writer to suggest that climate is a panacea for all chronic arthritis. On the contrary, we feel that no possible additional therapeutic aid should be neglected. However, there is sufficient evidence to show that carefully supervised climatic therapy is a potent factor and a valuable adjunct in the treatment of atrophic arthritis. Further studies are being made to determine what the essential factors in climate are, and to clarify their modes of action.

DISCUSSION

A single easy successful treatment for chronic atrophic arthritis is not yet available. It is not the intention of this writer to sound a pessimistic note, for we have reason to be most optimistic in the results secured by adequate treatment. We do, however, believe that it is time for the medical profession, as well as the victims of this unhappy disease, to recognize that there is no easy way. Every patient with chronic arthritis becomes an individual problem, and requires, in addition to full medical care, the ideal patient-physician relationship before there can be any hope of success. In any chronic illness the psyche must be considered, but the writer knows of no condition in which it plays a more important rôle than in chronic atrophic arthritis. The ideal treatment of this disease will require of the physician an enormous expenditure of nervous energy and the patience of Job, for there must be careful and methodical consideration of each individual problem. The management is made more difficult because of the mental depression so common to patients with this disease. They are often migratory, seeking always some new cure. The patients of our group had consulted an average of three different physicians or clinics before entering here. A tremendous advance in the therapy of this disease can occur if physicians will only stop treating these patients half-heartedly by every new or easy method recommended, and will tell them honestly what the problem of adequate treatment includes. There is little to choose between the physician who treats with an ointment the lump in a woman's breast, and the one who does not recognize or treat wisely the early manifestations of atrophic arthritis. Cancer, fortunately, kills its victims, but unchecked chronic arthritis leaves its victims a lifetime of crippling deformity and pain.

SUMMARY

1 One thousand patients with the various types of chronic arthritis were classified and studied. This paper is limited to a consideration of therapy in atrophic arthritis, of which there were more than 300 in this series.

2 After trying a very great number of therapeutic procedures, nearly all were discarded. The worthwhile methods are tabulated and discussed.

3 All patients were treated by general measures such as rest, exercise, heat, massage, prevention and correction of deformity, diet and bowel management. Indications and contraindications for these methods are enumerated.

4 Groups of patients after being treated by general measures for a control period, were given special types of therapy and over a period of several months or years, comparisons of results were made. Removal of foci of infection, transfusion, vaccine, and special climatic therapy were the special methods used on four comparable groups. The most striking result of this experiment was to prove the nonspecificity of any therapeutic agent tried.

5 Removal of foci is of value in the subacute or early chronic stage of the infectious "b" group. It has been found of little help in the "a" group and in the very chronic stage of the "b" group. Removal of foci is often disastrous unless adequate precautions are taken.

6 Blood transfusions were very helpful in a group of subacute and early chronic cases, but were of little value in the very chronic afebrile cases with advanced bone and joint changes.

7 Vaccine has a definite but limited place in the therapy of atrophic arthritis. No favorable results were secured from its use in the "a" type. In the "b" group, skin reacting autogenous organisms in minute desensitizing doses, intravenously, gave the most favorable results. It is believed that much harm is done by the indiscriminate injection of vaccines. The present practice of distributing stock vaccines to the general profession for the treatment of chronic arthritis is deplored.

8 Climate is believed to be a potent factor and a valuable adjunct in the treatment of atrophic arthritis. The following evidence is presented:

(a) There is a low incidence of atrophic arthritis in local Indians, as compared with similar tribes elsewhere.

(b) There is a low incidence of atrophic arthritis in native residents in the vicinity of the Tucson desert.

(c) In a group of 100 patients with atrophic arthritis, gratifying results were obtained in a large proportion without resort to any specific therapy other than the general measures described and climatic treatment. It is our belief that, inasmuch as most of these patients had tried nearly every other known remedy, the satisfactory results can in a large measure be ascribed to carefully supervised climatic therapy.

9 A plea is made to physicians to stop treating these patients with every new cure suggested, to recognize and treat wisely the early manifestations, and, above all, honestly to explain to the patient the numerous factors necessary to giving him adequate care.

THE INDICATIONS FOR COLLAPSE THERAPY IN PULMONARY TUBERCULOSIS¹

By I D BRONFIN, M D , F A C P , *Denver, Colorado*

THE literature of the past five years on the treatment of pulmonary tuberculosis, impresses one with the nearly universal enthusiasm for collapse therapy. Characteristic of the mechanical age in which we now live, the treatment of tuberculosis is rapidly being placed on a mechanical basis, in much the same way as the "go out West and rough it" formula was advocated by many four decades ago. That tuberculosis is primarily a constitutional disease with local manifestations is overlooked by many enthusiasts. Extravagant statistics, frequently compiled prematurely, attempt to prove the efficacy of favored surgical procedures, and premises have recently been advanced¹ to justify collapse therapy in every case of unilateral pulmonary tuberculosis. Such waves of enthusiasm for a new form of treatment are familiar phenomena in medical history, as is the aftermath of disillusionment, endless suffering and protracted invalidism. A conservative discussion, therefore, of the indications for the various types of collapse therapy, with the thought in mind that they are only aids and not specifics, is deemed advisable.

THE CURABILITY OF PULMONARY TUBERCULOSIS BY REST AND HYGIENIC LIVING

For clinical purposes, two types of pulmonary lesions need be considered, first, the acute or exudative type, characterized by a rapid onset with either limited pneumonic consolidation or scattered fluffy parenchymal deposits through one or both lungs, second, the proliferative type, insidious in onset, chronic from the start, slow in progression and with a pronounced tendency towards fibrous tissue formation. In favorable cases, healing occurs by resolution, that is by absorption of the exudate, or by fibrosis which encapsulates the disease and ultimately replaces it by scar tissue. If the disease is recognized before softening and excavation have occurred, regardless of the extent of the process, a large number of patients will recover under the old formula of rest, fresh air and good food. Physiologic rest is the keynote of treatment, aided by such additional measures as the education of the patient to suppress the cough, postural rest and the use of shot bags². It should be continued for as long a time as there is encouraging evidence of improvement. Striking as have been the results from pneumothorax and surgical measures when the rest regime has failed, the results from the latter

* Presented at the Seventeenth Annual Session of the American College of Physicians at Montreal, February 8, 1933.

From the National Jewish Hospital, Denver, Colorado, and the University of Colorado School of Medicine.

have in numerous instances been even more remarkable and more enduring. It would be a calamity if physicians and specialists, in their desire for short-cuts to success for their patients, forgot the inestimable value of rest treatment and its underlying principles. Upon these principles, after all, are based all the modern procedures of collapse therapy.

For a reasonably accurate determination of a patient's progress when on a conservative regime of treatment, clinical observation alone is not always a reliable guide. Progressive caseation-necrosis with cavity formation is not incompatible with a normal pulse and temperature. There need not necessarily be even an increase in cough and sputum or a loss in weight. Serial roentgenograms taken at intervals of three or four months and more frequent fluoroscopic observations are therefore of paramount importance. Of nearly equal value are hematologic studies, notably the erythrocyte sedimentation test and the determination of the leukocyte-lymphocyte ratio. A persistently high sedimentation rate and a leukocytosis with a high polynuclear count in the absence of non-tuberculous inflammatory conditions, call for a painstaking search for tuberculous involvement of other organs. If the explanation is not found in the presence of such a complication the suspicion should be aroused that the disease in the lungs is not pursuing a favorable course despite apparent general improvement. If the indications furnished by these laboratory methods when properly coordinated with the clinical manifestations are followed, the average patient who comes under medical care before cavitation has formed has more than an even chance to recover under a conservative plan of treatment.

THE HIGH INCIDENCE OF ADVANCED CASES

It is, however, a sad fact that over 75 per cent of patients are already in the moderately advanced or far advanced stages of the disease, frequently with extensive cavitation, before they apply for treatment to the qualified physician or institution. Mistakes in diagnosis and haphazard treatment, or neglect, fear or ignorance on the part of the patient account for this condition. The practice of many county and state tuberculosis sanatoria of not housing patients for more than six or nine months, and the failure of social agencies properly to bridge the gap between sanatorium life and the competitive world are also important factors, and must annually be responsible for thousands of advanced cases which can no longer be cured by natural methods. These are the patients for whom artificial aid is indicated. Cavities exceeding the size of five centimeters in diameter rarely become obliterated from rest alone. Untreated, a number of them may retain for a time a certain degree of physical efficiency, but the majority are chronic invalids and ultimately die in from four to six years.

The main problem, obviously, is the advanced case. The National Jewish Hospital at Denver recruits patients from every State in the Union and Canada. The average duration of the pulmonary disease in these cases

is five years, and 75 per cent of them have already had one or more residences of varying length in hospitals or sanatoria. Over 70 per cent of these patients present on admission evidence of far advanced fibro-cavernous pulmonary tuberculosis. In brief, our material is composed chiefly of tuberculous derelicts who have gone through the mêlée and have scored once or several times apparent victories but have failed to attain the goal. A critical analysis of the history and clinical course of each individual case discloses an appallingly large incidence of relapses, due often, it is true, to the adverse economic conditions which are the lot of the average consumptive, but often also attributable to ineffective treatment. The assertion¹ that nearly every far advanced case has at one time in the course of his disease been suitable for some form of collapse therapy is well borne out by a study of the material at our disposal. It is because so many cases present the tragic story of lost opportunities, often through no fault of their own, that the question of the advisability of collapse therapy has come to be our first consideration following the initial examination of a tuberculous patient. The fact that we have been successful in securing marked amelioration of symptoms and many cures in a considerable number of apparently hopeless cases, has enabled us to offer a more favorable prognosis to those who only a decade ago were considered beyond medical aid.

MAXIMUM TIME-LIMIT FOR CONSERVATIVE TREATMENT

It is realized that individualization is one of the most important requisites to intelligent treatment. Not until a specific remedy is discovered will there be a therapeutic measure applicable alike to all patients with tuberculosis. Nevertheless, the following axioms may be safely formulated. A patient between the ages of 15 and 50, not in the terminal stages of the disease and free from grave tuberculous or non-tuberculous complications, who fails to improve in six months under a properly conducted rest regime should be considered as a possibly suitable subject for collapse therapy. Serious symptoms, such as recurring hemoptyses, or physical and roentgen evidence of beginning cavitation, justify resorting to collapse measures at an earlier date. If the disease is of one year's duration or longer, and rest treatment has already been tried elsewhere, one or two months of observation should suffice to determine the type of new treatment indicated. Procrastination is fraught with dangerous possibilities² and physicians have more frequently regretted³ not having instituted pneumothorax than having started it too early.

PRINCIPAL TYPES OF COLLAPSE

The three methods of collapsing a diseased lung, in the order of their importance and range of applicability, are (1) artificial pneumothorax, (2) phrenicectomy, (3) thoracoplasty. The aim of each method is identical in every respect, namely, to relax or collapse the affected lung sufficiently to promote a maximum of healing by either resolution or fibrosis, and to

prevent metastatic spread of disease and hemoptysis by obliterating discharging cavities. However, owing to the fact that each method has its distinct advantages, disadvantages and limitations, their respective indications must be considered separately.

INDICATIONS FOR ARTIFICIAL PNEUMOTHORAX

A useful rule by which to be guided in choosing a type of collapse therapy to fit the individual case is the simplicity, effectiveness and flexibility of the procedure. Pneumothorax excels in these advantages and should, therefore, be tried first before other methods are undertaken. The technic of administering filtered air into the pleural cavity is easy, although considerable skill and judgment are necessary in the general management of these cases, and particularly in treating such complications as effusions, empyema, adhesions and, rarely, air embolism. In the absence of pleural adhesions, a better collapse of the lung can be secured by artificial pneumothorax than by any other method. There is very little reaction following the initial treatment, and practically no untoward effect in uncomplicated cases after subsequent air refills. The indications may conveniently be divided into *absolute* and *provisional*. The *absolute* indications are

- 1 Extensive unilateral exudative or fibro-caseous pulmonary tuberculosis, with or without recognizable cavitation by physical signs or the roentgen film. Bacillary sputum of 15 cubic centimeters or more in twenty-four hours usually indicates cavitation. The more definite and the more extensive the cavitation, the more cogent is the indication.

- 2 Chronic unilateral fibro-ulcerative tuberculosis, with cavitation ranging in size from three to five centimeters in diameter, even if constitutional symptoms are absent. The only effective insurance against a bronchogenic spread of the disease to the uninvolved lung is closure and final obliteration of cavities.

- 3 Profuse hemorrhage or recurrence of pulmonary bleeding when the source of the latter is ascertained with a reasonable degree of accuracy. While hemoptysis, as a rule, stops of its own accord, the institution of pneumothorax is justified when hemostasis cannot be secured by medicinal measures, or when the bleeding recurs and constitutes a danger of either exsanguination, spread of the disease or aspiration bronchopneumonia. Too much consideration should not be paid to the condition of the contralateral lung even if extensively diseased. Without pneumothorax the danger to life is decidedly greater.

- 4 Acute unilateral pneumonic tuberculosis. If the constitutional symptoms are marked and the toxemia is profound, excavation may occur in as short a period as one week. This can be prevented by the early collapse of the lung. On the other hand, if the symptoms are mild, watchful waiting is permissible, provided frequent roentgenoscopic and roentgenographic examinations constitute an essential part of the clinical observation.

The *provisional* indications are:

1 Bilateral disease with unilateral single or multiple cavitation The frequency with which most pneumothorax operators have seen marked clearance of the lesion in the better lung following the successful collapse and closure of cavities in the more diseased lung warrants this recommendation for selected patients whose general condition is still good and who present other evidence of some degree of natural immunity The contralateral disease must not be of the acute pneumonic or exudative type, but scattered proliferation with small patches of exudation frequently undergo resolution after the subsidence of the constitutional symptoms and the reduction in cough and sputum which so often follow a successful pneumothorax It is fallacious to speak of an extra physiologic burden thrust upon the better lung in connection with pneumothorax therapy In a properly managed pneumothorax uncomplicated by pleural adhesions, only the major diseased portion of the lung, as a rule, need be collapsed, while the lower, less involved area is only relaxed and is partially functioning Furthermore, where one lung is extensively involved, the chief burden of respiration is already carried on by the contralateral lung Finally, the reduction of toxemia and the subsidence of the traumatizing cough materially aid the better lung to function with a minimum of embarrassment

2 Bilateral disease with extensive cavitation in one lung and small, thin-walled upper lobe cavitation in the other lung Untreated, the majority of patients with such type of involvement are doomed Rest alone rarely suffices The cautious collapse of the more diseased lung frequently aids not alone in improving the condition of the contralateral lung, but in closing such early limited cavitations as it contains This obtains especially in cases where the mediastinum is flexible, as the slight or moderate displacement of the mediastinum toward the less affected lung causes a certain degree of splinting and relaxation of that lung This compression of the less affected lung constitutes an added important contributing factor to the healing process

3 Bilateral pneumothorax When a case such as described under the last heading fails to improve after a satisfactory collapse has been established, and there is reason to believe that the symptoms are now due to unchecked activity or progression of the disease in the contralateral lung, simultaneous bilateral pneumothorax is justified Experience has shown that young individuals between the ages of 15 and 30, whose disease is of relatively short duration, and in whom there is no evidence of myocardial impairment, tolerate bilateral pneumothorax very well It is, in selected instances, as compatible with a useful and efficient life as unilateral pneumothorax However, this is true only of those patients in whom the physician is fortunate enough to obtain a selective collapse of the upper lobes, where the disease is usually localized, and only a slight relaxation of the lower lobes which will not interfere with their proper physiological function

4 Chronic fibro-cavernous disease of one lung and more recent acute

disease in the other lung. If, after a regimen of rest for two or three months without improvement, physical examination and the roentgen film disclose a stationary condition of the older excavated lesion but progression and early cavitation in the better lung, it is good judgment to collapse the latter with the thought in mind that after a year or two of such treatment the lung may be safely reexpanded and attention then paid to the problem of the primary diseased lung. Such a procedure is logical and has proved useful in preventing the occurrence of extensive bilateral cavitation for which there is admittedly no remedy.

5 Alternating pneumothorax. Acute contralateral disease during pneumothorax therapy is a grave complication and is responsible for a high mortality.⁵ A collapse of the newly involved lung is permissible if the patient is otherwise suitable for such treatment. On the other hand, where the first pneumothorax has already been maintained for two years or longer with cavitation apparently closed, it is much safer to allow that lung to reexpand either before collapsing the other lung or as soon as the collapse is initiated. Alternating pneumothorax⁶ has proved of much value in patients past the age of 30 and in younger individuals in whom simultaneous collapse is contraindicated because of evidence of myocardial insufficiency.

MECHANICAL AND PHYSIOLOGICAL FACTORS RESPONSIBLE FOR BENEFICIAL RESULTS FROM PNEUMOTHORAX

The interposition of several hundred cubic centimeters of air between the parietal and visceral pleura at once reduces the effectiveness of an adhesive force, the normally existing negative intrapleural pressure, which greatly militates against adequate rest for a diseased lung. At the same time, this air splint relaxes the elastic tissue of the lung which is greatly stretched during each inspiration. The elimination or reduction of the negative intrathoracic pressure and the overcoming of the elastic recoil of the lung are the most important and the most effective mechanical factors in securing the additional much needed rest for the involved lung. Following several air refills, the lung is more immobilized and its respiratory activity reduced to a minimum. As the lung becomes reduced in volume, the secretions diminish as they are more easily eliminated, and the cavitation gradually closes. The almost dramatic suddenness with which improvement sets in is said to be due to a decrease in toxic absorption from the diseased area as a result of lymph stasis and diminished blood supply. The continuous increase in fibrous tissue during the time the lung is collapsed aids greatly in the encapsulation and healing of scattered diseased areas.

END-RESULTS OF PNEUMOTHORAX

Our experience coincides with that of Amberson,⁷ Peters,⁸ Packard⁹ and others. An effective pneumothorax, properly managed and maintained for three years or for a minimum of one year from the time the sputum becomes

negative for tubercle bacilli, will cause an arrest of the disease in from 75 to 85 per cent of patients and restore them to normal working ability. In the average case, one year of hospitalization or rest at home is sufficient to enable the patient to return to a useful life provided the gas refills are continued at stated intervals. Three times as many patients are known to be alive two to fourteen years after treatment by pneumothorax as have survived from those in whom pneumothorax was attempted without success on account of failure to find a pleural space. Three times as many pneumothorax patients are leading a normal existence.⁸

Nevertheless, it is important to point out the large incidence of pleural complications of pneumothorax therapy. As we have pointed out elsewhere,³ these complications are in direct proportion to the extent and duration of the pulmonary disease. In a series of 176 patients in whom we induced pneumothorax during the past five years, 65 per cent had serous effusions, 18.7 per cent purulent effusions, and 5 per cent died ultimately from empyema. This indicates that pneumothorax, while in itself a simple procedure, has an ultimate mortality of from 3 to 5 per cent, assuming that in early cases the occurrence of empyema is less frequent. Based upon these figures, an eloquent plea could be made for more conservatism. However, long experience has shown that the majority of those patients in whom pneumothorax or other collapse measures are indicated and for some reasons are not performed die after varying periods of invalidism and intense suffering. The present day physician who does not avail himself of modern surgical treatment in properly indicated cases is unjust to his profession and harmful to his patients.

IMPEDIMENTS TO GOOD RESULTS

The first and most important hindrance is pleural symphysis. In 26.3 per cent of our patients upon whom pneumothorax was attempted, no space was found after several explorations in different localities. When a space is found and string-like adhesions are present, they can be stretched sufficiently in the majority of patients by the cautious continuation of gas refills to eventually effect a good collapse without resorting to intrapleural pneumolysis.¹⁰ According to a recent report,¹¹ Unverricht himself is doing now one operation for the division of adhesions where he did ten five years ago. The dangers of hemorrhage, pleural effusion, or perforation of a cavity with the subsequent development of empyema, must always be considered in connection with intrapleural pneumolysis, notwithstanding the successful results reported by some authors.^{12, 13} In our experience, clear cut indications for pneumolysis are found in not more than 3 per cent of pneumothorax patients. By utilizing phrenicectomy to relax these adhesions, that figure can be greatly reduced.

The thick-walled cavity is another cause for pneumothorax failure. The lung in such instance may be seen well collapsed, but the cavity remains

patent because of failure of the thick wall surrounding it to yield to external pressure. String adhesions are frequently seen radiating from such cavities toward the chest wall, but their severance with the cautery fails to close the cavities, for the problem is not so much the adhesions as the thick wall itself.

More of an obstacle than string adhesions or even thick-walled cavities are broad-band adhesions which completely prevent a collapse of the lung above the third or second rib, i. e. at a level where the lesions are nearly always associated with cavitation. Here the object of the pneumothorax is entirely defeated, unless there is considerable pulmonary involvement below the level of the adhesions, in which event the patient may obtain for a time marked symptomatic relief. However, since the main objective is the closure of cavities, it has become our practice not to continue pneumothorax with uncollapsed cavities for more than one year, even if satisfactory palliative results have been obtained, without urging the patient to submit to other surgical procedures. The dangers of an uncollapsed cavity, besides hemorrhage or metastasis to the better lung, are not sufficiently appreciated by otherwise experienced pneumothorax operators. Most of our fatal empyema cases with bronchial fistulae that have come to autopsy have shown tears in a cavity wall which probably would not have occurred if pneumothorax had not been continued too long. It has long been our contention that a cushion of air interposed between the chest wall and the lung is not nearly as good a support to a diseased lung as the chest wall itself. This is the most likely reason for the greater frequency of spontaneous pneumothorax during the course of induced pneumothorax,¹⁴ and it is not improbable that many pleural effusions are caused by small-sized unrecognized pulmonary perforations. It is because of these dangers and the failure to achieve the main objective that patients with partial and incomplete pulmonary collapse have to be submitted to more radical surgical treatment.

PHRENICECTOMY

As statistics accumulate and the longer phrenicectomized patients are observed, it becomes clear that the value of phrenicectomy has been much over-rated. In our series¹⁵ of 183 patients, an arrest of the disease from this procedure alone was obtained in only 12 or 6.6 per cent. It is also of importance to note that of the seven patients who had unilateral lesions either without, or with doubtful cavitation, only four showed an arrest of the disease when examined at the end of from one to three years. It is difficult to reconcile our results with the teaching of those¹⁶ who advocate phrenicectomy in preference to pneumothorax for all patients with unilateral lesions, without even affording them the benefit of a six months period of conservative treatment. It is generally conceded that pneumothorax carries with it greater dangers and that it is a much more tedious and protracted treatment than phrenicectomy, but the comparative results of the two methods are evidently a matter of individual experience. Statistics are decidedly mis-

leading unless accompanied by a detailed description of the material studied. As a means of closing well formed apical cavities, phrenicectomy has definite and marked limitations, although occasionally a surprisingly good result is obtained. Nevertheless, phrenicectomy has a wide range of usefulness. Its value is notable in the following conditions in the order named:

- 1 As a palliative measure to control excessive cough, especially of the emetic variety, and copious tenacious expectoration in cases which present bilateral lesions with only limited cavitation in the better lung. In from 40 to 50 per cent of patients, the decrease in cough and sputum, the greater ease of expectoration, and the general improvement are quite marked and constant effects.

- 2 As a curative measure for chronic, unilateral, lower lobe, tuberculous or non-tuberculous lesions. The first simple sectioning of the phrenic nerve by Stuert¹⁷ was undertaken to meet such an indication, and for a time the operation was applicable only to lower lobe lesions. It is ineffective in lower lobe pneumonic phthisis and in bronchiectasis of long standing, and often aggravates these conditions.

- 3 To control profuse or recurring hemoptysis when pneumothorax cannot be induced.

- 4 To supplement pneumothorax by relaxing adhesions which prevent an effective collapse.

- 5 As a substitute for pneumothorax, when a free pleural space is not available, in cases of predominantly unilateral lesions of the subacute or chronic variety. In acute pneumonic tuberculosis it seems of little or no value.

- 6 In tuberculous empyema with or without bronchial fistula when thoracoplasty is contemplated. Occasionally, the latter is obviated following an ascent of the diaphragm with a consequent decrease in the size of the empyema pocket, and sometimes there also occurs a closure of the fistula.

- 7 As a measure preliminary to thoracoplasty, not so much to test the efficiency of the contralateral lung, as to improve the general condition of the patient and to make him a safer operative risk. However, where there is a giant upper lobe cavity and the lower half of the lung shows little or no involvement, a high ascent of the diaphragm sometimes causes stagnation of secretions in the cavity, and the latter increases in size.

To the skillful surgeon, a phrenicectomy is a minor operation. It is done under local anesthesia and usually takes not more than fifteen minutes for its completion. The patient's balance, no matter how delicate, is, therefore, rarely disturbed from the operation per se. While we¹⁵ have had no direct operative mortality, a postoperative mortality, that is, death within one to two months after the operation, has been experienced in 27 per cent of our series, in contrast with 12 per cent reported by Berry¹⁸. This difference is due principally to insufficient caution employed by us in the selection of patients, some of whom were virtually terminal cases. It is a decided error to submit a patient to an operative procedure, even if it be of a minor char-

acter, on the basis that it is his only chance or that he has nothing to lose. If such a patient fails to obtain the desired result, or rapidly becomes worse and dies shortly after the operation, the latter gains local disfavor and other patients ideally suited for such an operation are reluctant to accept it.

THORACOPLASTY

Since pneumothorax is available to only 15 per cent of patients as we see them, notwithstanding the wide range of indications, and since phrenicectomy is a curative measure in the same type of patients to the extent of only 6.6 per cent, it would seem that thoracoplasty should have a large field of applicability. Actually, this is not the case. Only 4.6 per cent of those patients treated unsuccessfully by pneumothorax were found by us suitable for thoracoplasty. Theoretically, the patient with a unilateral exudative lesion in whom pneumothorax cannot be induced should be ideally suited for thoracoplasty, but experience has taught otherwise. An operation of this type when the patient is in the stage of defense often leads to disastrous results. It is only when the acute stage with high fever, rapid pulse and other toxic manifestations has passed, and the patient is still not making satisfactory progress, that thoracoplasty may be undertaken.

The compromises which may be made with the contralateral lung in pneumothorax practice are absolutely forbidden in thoracoplasty. The trauma which ensues to the patient from the latter procedure may cause a reactivation of latent foci in the contralateral lung. It is, therefore, a good rule to defer thoracoplasty for at least a year from the time when the better lung last showed clinically or roentgenographically an active focus of disease. Although a report has recently been made¹⁹ on the feasibility of bilateral upper stage thoracoplasty, it is doubtful whether such a radical measure will gain popular favor, for the reason that resection of the upper five ribs alone without pneumolysis rarely obliterates a thick-walled cavity, and also because there is forever the danger of a reactivation or spread of the disease in the untreated lung by the time the patient has sufficiently convalesced from the first operation. Not until a simpler surgical technic is elaborated will it be safe to deviate from the accepted conservative indications, especially with regard to the qualifications of the better lung.

SALIENT POINTS TO BE CONSIDERED IN THE SELECTION OF PATIENTS FOR THORACOPLASTY

1 *Resistance* This implies a careful review of the patient's previous clinical course, the severity and frequency of relapses, how readily he responded to rest treatment, and such other pertinent data as might show a satisfactory degree of resistance to the disease. If there is no evidence of past or present resistance, the operation should be deferred.

2 *Physical Examination* A clear contralateral lung as determined by the roentgen-ray is in itself not sufficient. Significance should be attached to

localized crepitant or subcrepitant râles elicited after cough in the hilus region or at the base of the better lung even when the roentgen film discloses no definite lesion. In one such case with basal râles a fatal termination from contralateral lower lobe involvement occurred two months after the completion of the third stage. The serial roentgen-ray films had given us a false sense of security, so that the auscultatory findings were too lightly regarded. The importance of careful and repeated chest examinations, preferably by more than one clinician, cannot, therefore, be over emphasized.

3 *Myocardial Integrity* It is realized that even with all the instruments of precision now at our disposal it is exceedingly difficult to estimate a patient's cardiac reserve. Nevertheless, by means of a carefully taken history, and from the study of the pulse rate at rest, in the recumbent and upright positions, and following graded exercises, it is possible to form a reasonably accurate judgment as to the burden carried by the heart and as to the heart's ability to stand the immediate strain of a drastic operation and to later successfully accommodate itself to the intrathoracic changes occurring after a complete thoracoplasty. The blood pressure is an important guide. A pulse rate persistently above 100 with the patient at rest, and a systolic blood pressure below 100 are strongly suggestive of myocardial insufficiency.

4 *The Roentgenogram* A study of serial films taken over a period of months or years is of the greatest help in determining accurately those mechanical factors interfering with healing which have recently been classically described by Pottenger²⁰. An accurate knowledge of these mechanical factors enables the observer to decide upon the type and extent of the surgical operation. Not alone that—it visualizes the type of existing pathology, and shows whether the lesion is predominantly proliferative or exudative. The more it is proliferative, the greater the resistance. Finally, the film gives valuable information regarding the condition of the contralateral lung. The presence of a roentgen lesion without physical signs is a more frequent clinical experience than is the presence of physical signs without a demonstrable roentgen lesion.

From a study of these special features, the indications for thoracoplasty become clear-cut and logical. Briefly, they are

- 1 Unilateral chronic fibro-ulcerative tuberculosis, in which conservative measures have failed and in which pneumothorax and phrenicectomy have proved ineffective

- 2 The same type of lesion, with a limited contralateral involvement which has not been active for over a year

- 3 Unilateral chronic cavitation when simpler measures have failed

- 4 Recurring hemoptysis when the source of the bleeding is definitely ascertained and the contralateral lung is not under suspicion

- 5 Tuberculous empyema when there is no tendency of the lung to re-expand following frequent aspirations. The presence of a bronchial fistula demands early intervention. A preliminary phrenicectomy is worth trying, as occasionally it alone closes the perforation and the lung thereafter slowly

reexpands. If this does not occur within one or two months, there is very little to be gained from further waiting, especially if there is considerable toxic absorption. A moderate amount of chronic disease even with limited cavitation in the contralateral lung is not a contraindication to thoracoplasty for tuberculous empyema, for without operation the prognosis in this condition is invariably poor.

LIMITATIONS OF POSTERIOR PARAVERTEBRAL THORACOPLASTY

Since the major objective in the treatment of chronic pulmonary tuberculosis is the obliteration of pulmonary cavities, a thoracoplasty can be said to fail in its purpose if it does not effect this result. In 50 per cent of our thoracoplastic patients, although their general condition had greatly improved and many had attained normal working ability, there was a persistence of a small amount of bacillary sputum. No patient can be considered out of potential danger as long as the sputum remains positive for tubercle bacilli. Thick-walled apical cavities, and centrally located cavities with thick walls and a very thickened pleura are the principal causes for an imperfect collapse. Regeneration of the ribs, if the intervals between the stages of the operation have to be unduly prolonged on account of infection or the poor condition of the patient, frequently prevents a complete collapse. Anterolateral costectomy is advocated by Hedbloom²¹ to meet such contingencies. It is applicable alike to incompletely collapsed pulmonary and to empyema cavities. This type of secondary operation will, in time, be more widely employed as the danger of imperfectly collapsed cavities comes to be more generally recognized. Our problem has been to convince the patient of the necessity of further surgery when he is enjoying good health and is free from symptoms except for the morning cough and slight expectoration. To obviate the possibility of a secondary operation, Bruns and Casper²² have devised a new technic which is essentially a combination of an upper stage thoracoplasty and pneumolysis. It seems ideally indicated for an upper lobe lesion with a large thick-walled cavity. In our personal experience with two cases in which this operation was employed, the results have been very gratifying. For selected cases it will probably become the operation of choice.

CONTRAINDICATIONS TO COLLAPSE THERAPY

Although certain conditions interdicting the collapse of a lung by one of the three principal methods have already been touched upon, the general subject of contraindications is deserving of a separate discussion. The average patient between the ages of 15 and 50 with unilateral or nearly unilateral pulmonary disease rarely presents contraindications to pneumothorax. With the advent of insulin, diabetes no longer precludes pneumothorax. Our experience with pneumothorax in relatively young diabetics during the past five years has been gratifying. This does not hold true of

thoracoplasty. Dyspnea, if not toxic, cyanosis, emphysema and decompensated valvular heart disease contraindicate any form of collapse therapy. Well compensated mitral regurgitation is usually not a contraindication. In bronchial asthma, pneumothorax may be cautiously tried, possibly also phrenicectomy, but not thoracoplasty. In nephritis without evident impairment of the cardio-vascular system the two simpler measures are permissible. If renal function and blood chemical determination are within normal limits, thoracoplasty may be considered. Laryngeal tuberculosis, if not acute, and if not merely a local manifestation of miliary tuberculosis, does not contraindicate any form of collapse measure. In intestinal tuberculosis, if not too far advanced, pneumothorax or phrenicectomy may be employed but not thoracoplasty, unless the intestinal disease has been inactive for at least one year. Patients past the age of 40 do not tolerate collapse therapy well, especially thoracoplasty, yet, this is not an inflexible rule. A patient at the age of 45 or even 50 who has not been sick for more than five years and who, during that time, has had periods of remission enabling him to be up and about for several months at a time is often a better surgical risk than another patient 30 years old who has been sick 10 years and has been confined to bed the greater part of that time. As a matter of fact, it has been our practice, whenever we receive a patient who is suited for thoracoplasty and who has been confined to bed elsewhere for some time, to wean him gradually away from the bed and to assign him graded walking exercises for several weeks before proceeding with the operation, unless indeed the latter has to be done to meet an emergency, such as hemoptysis. Prolonged bed rest in patients of this type often causes a lowering of general muscular and myocardial tone. It is the flabby, irritable heart that constitutes one of the main dangers. The psychic state of the patient is also an important consideration. A fear-complex requires painstaking effort on the part of the clinician to overcome, not by coercion or persuasion, but by education. Close association between the successful postoperative case and the candidate for operation is often more helpful in overcoming the latter's apprehension than are the physician's efforts.

RESULTS OF THORACOPLASTY

In only 2.4 per cent of all our patients, and 4.6 per cent of our unsuccessful pneumothorax cases, was thoracoplasty deemed a feasible procedure. In the desire to be of assistance to an otherwise doomed patient, certain relative contraindications were occasionally disregarded. That is probably why our results do not compare favorably with those of others. Our operative mortality, within one to four weeks, was 12 per cent. By a more rigid selection of cases, this figure has been reduced in the past year to a little over 7 per cent. Approximately 50 per cent have either experienced an apparent arrest of the disease, or have improved to such an extent as to enable them to do full time work. The observation period after the opera-

tion ranges from one to twelve years. In from 25 to 30 per cent of patients, in spite of improvement, varying degrees of invalidism persist. The cause of the invalidism in these cases is usually either the continuance of low grade tuberculous activity attributable as a rule to an incompletely collapsed cavity, or the presence of myocardial insufficiency or emphysema. The occurrence of new disease foci or the reactivation of old foci in the better lung has been very rare, especially in those whose sputum became free of tubercle bacilli. The results, therefore can be said to be excellent when one considers that these patients are at best sub-standard surgical risks. Considering the further fact that there is nothing else to offer them except several years of a hopeless sanatorium existence while they are waiting for the finale, thoracoplasty is a real boon to the far advanced case.

SUMMARY

For over 13 years we have been employing collapse therapy in patients, the average duration of whose pulmonary disease has been five years, and of whom 70 per cent were far advanced cases with cavitation. In the past six years, the indications were extended and relative contraindications have been occasionally disregarded. Nevertheless, pneumothorax was applicable in only 15.67 per cent, phrenicectomy as an independent or supplementary procedure in 19 per cent and thoracoplasty in 2.4 per cent. Of 239 patients in whom pneumothorax was attempted, 63 or 26.3 per cent had complete pleural adhesions so that even a pocketed space could not be obtained. Since 75 per cent of all patients had had previous institutional or private treatment elsewhere, these figures would seem to indicate that either collapse therapy is not instituted early enough to make it of greater value or that many patients discharged as cured were actually only quiescent cases which later sustained relapses no longer amenable to rest treatment. Withal, our results have been essentially very satisfactory. Collapse therapy is justly considered the greatest achievement in the field of tuberculosis during the past two decades. It has made advanced pulmonary tuberculosis a treatable disease. To the properly selected patient, it offers a chance of recovery far greater than that which he can expect from any other form of treatment. It shortens the duration of the disease and makes recovery more certain. In the average patient, the choice of procedure should be first pneumothorax, second phrenicectomy, and third thoracoplasty. A patient under conservative treatment, even if he pursues a clinically favorable course, should have frequent roentgen-ray chest examinations and blood studies, especially erythrocyte sedimentation tests, to determine more accurately whether Nature's method is wholly adequate. If the indications for collapse therapy are favorable, it should be instituted without delay and before extension of the disease makes the patient unsuitable for such treatment.

The indications and contraindications have been emphasized, for they constitute the most important guides in the management of the advanced

case, though as yet no set rules are possible. The individualization of patients will always be essential to intelligent treatment, and above all clinical judgment is necessary. A knowledge of pneumodynamics is indispensable to both physician and surgeon, and both must render each other the closest cooperation in order to secure the best possible results for their patient. Finally, the psychological make-up of the patient must be carefully scrutinized and all hidden fears, doubts and prejudices unravelled and overcome. In no disease does the personal element, the tact, the kindness of the physician, his willingness to give freely of his time to the patient count for as much as in tuberculosis. To be able to break unpleasant news in such a way as to make the patient see the more hopeful aspect of a perplexing situation is an art which can be acquired. It is the duty of the physician to inspire in his patient confidence in a proposed new form of treatment without necessarily concealing its hazards or actual dangers, and experience teaches how to do it. We confidently believe that by following closely such a program it is possible to obtain satisfactory results in even as unfavorable a disease as far advanced chronic pulmonary tuberculosis.

REFERENCES

- 1 HEAD, J R, and SCHLACK, O C. A programme for collapse therapy, *Am Rev Tuberc*, 1931, xxiv, 42-45
- 2 WEBB, G. Rest and shot bags in pulmonary tuberculosis, address before 62nd Annual Session of Colorado State Medical Society, Sept 9, 1932
- 3 BRONFIN, I D, NELSON, E, and ZARIT, J. Artificial pneumothorax, a plea for its wider application in the treatment of pulmonary tuberculosis, *Am Rev Tuberc*, 1925, xii, 197-208
- 4 BROWN, L, and HAYES, J N, in TICE. Practice of medicine, Vol II, 1927, W P Pryor Co, p 524
- 5 RIST, E. Results of artificial pneumothorax in pulmonary tuberculosis, *Am Rev Tuberc*, 1927, xv, 294-305
- 6 BRONFIN, I D. Alternating artificial pneumothorax, *Am Rev Tuberc*, 1931, xxiii, 661-672
- 7 AMBRERSON, J B, JR. The indications for and the results of artificial pneumothorax treatment in pulmonary tuberculosis, *ANN INT MED*, 1930, iv, 343-347
- 8 PETERS, A. Artificial pneumothorax at the Loomis Sanatorium over 14 years, *Am Rev Tuberc*, 1928, xvii, 348-373
- 9 PACKARD, E N. The present status of 100 pneumothorax patients after from one to eighteen years' expansion of the lung, *Jr Thorac Surg*, 1932, i, 581-586
- 10 O'BRIEN, E J. The suspended cavity in artificial pneumothorax, *Am Jr Thorac Surg*, 1932, i, 603-611
- 11 DOLLY, F S. The present-day surgical treatment of certain diseases of the chest, *South-west Med*, 1931, xxv, 13-19
- 12 MATSON, R C. The cauterization of adhesions in artificial pneumothorax by the Jacobaeus-Unberriicht method of closed pneumolysis, *Am Rev Tuberc*, 1929, xi, 233-305
- 13 WELLES, E S. The result of cautery pneumolysis of adhesions complicating artificial pneumothorax, *Jr Thorac Surg*, 1932, i, 601-602
- 14 BRONFIN, I D. Spontaneous pneumothorax during the course of artificial pneumothorax, *Am Rev Tuberc*, 1924, ix, 346-363

- 15 BRONFIN, I D, and CHERNYK, M The value and limitations of phrenicectomy in advanced pulmonary tuberculosis, *Am Rev Tuberc*, 1932, xxvi, 689-708
- 16 HEAD, J, SCHLACK, O C, and MARX, J A statistical estimation of the value of a programme for collapse therapy, *Am Rev Tuberc*, 1932, xxvi, 653-664
- 17 STUERTZ, E Kunstliche Zwerchfellahmung bei Schweren Chronischen Einseitigen Lungenerkrankungen, *Deutsch med Wchnschr*, 1911, xxxvii, 2224-2225
- 18 BERRY, F B The unfavorable effects of phrenicectomy, *Arch Surg*, 1930, xxi, 1125-1133
- 19 ALLEN, D S Bilateral partial thoracoplasty for bilateral pulmonary tuberculosis, *Jr Thorac Surg*, 1932, i, 587-600
- 20 POTTENGER, F M Interfering mechanical factors in the healing of pulmonary tuberculosis, *Am Rev Tuberc*, 1932, xxvi, 229-234
- 21 HEDBLOOM, C A Anterolateral costectomy for inadequate collapse following posterior extrapleural thoracoplasty, *Arch Surg*, 1930, xxi, 1114-1124
- 22 BRUNS, E H, and CASPER, J The present status of chest surgery in the treatment of pulmonary tuberculosis, *Am Rev Tuberc*, 1932, xxvi, 665-688

CALCAREOUS AORTIC VALVULAR LESIONS*

By BURR M HATHAWAY, A B , M D , *Ann Arbor, Michigan*

STENOSIS of the aortic valve, with calcification, continues to attract the attention of clinicians and pathologists. The frequency with which this condition is found at autopsy, in contrast to the infrequency of its clinical diagnosis, and the unsettled state of opinion as to its etiology invite further study. To this end, 52 examples of aortic valvular disease have been selected from 4000 consecutive autopsies, these have been divided into significant groups, and subjected to clinico-pathological analysis. The results of this statistical study justify certain conclusions as to the etiology of this form of cardiac disease.

SURVEY OF LITERATURE

Aortic stenosis with calcification has been reported frequently and discussed from various points of view. Some of these case reports are presented without conclusions as to etiology.

LECLERC,¹³ in 1905, reported two cases of aortic stenosis in which the maximum murmur was heard at the left of the sternum instead of in the usual aortic area. The other physical findings in both patients were typical of aortic stenosis and the diagnosis was verified by autopsy, both cases having a marked stenosis due to fusion and calcification of the cusps. The author accounted for the unusual location of the aortic murmur by leftward displacement of the heart.

CABOT,⁴ in 1926, described a man of 47 years who had had a slowly progressing cardiac lesion since youth. At the time of admission he was *in extremis* and, with other murmurs, he had the typical murmur and thrill of aortic stenosis. Autopsy revealed aortic endocarditis with calcification, stenosis and insufficiency.

In 1931 TUOHY and ECKMAN¹⁰ reported six cases of aortic stenosis, three of which had come to autopsy and these showed calcareous nodules in the cusps. These authors observed that there is associated with this type of aortic stenosis a demonstrable degree of insufficiency, that the valvular deformity is due to nodular calcium deposits in the media of the cusps, that this lesion may produce typical anginal attacks in the absence of any coronary lesions and that no other valvular lesion produces such marked left ventricular hypertrophy. They diagnosed the presence of the calcareous nodules during life.

Another group of writers have favored senile, or non-inflammatory, changes.

In 1904 MONCKEBERG¹⁵ discussed thoroughly the microscopic anatomy of the aortic valve in an attempt to explain the occurrence of sclerosis and calcification. He presented four groups of patients who did not die of cardiac disease but who showed at autopsy varying degrees of sclerosis of the aortic valve. He demonstrated, to his own satisfaction, that there is no direct association between atherosclerosis of the first

* Received for publication March 20, 1933.

From the Department of Pathology, University of Michigan, Ann Arbor, Michigan, C V Weller, Director.

part of the aorta and aortic endocardial sclerosis, but that the latter process, like the former, is a senile degenerative change

In 1926 CLAWSON, BELL and HARTZELL⁸ studied 15 hearts showing aortic stenosis due to calcareous nodules, with no satisfactory evidence of inflammatory origin. The position of these calcareous nodules did not correspond to that of the vegetations in active endocarditis and almost invariably the root of the aorta in these hearts was free from sclerotic lesions. Microscopically, the lesions consisted chiefly of masses of calcium salts, and decalcification left a homogeneous material. The surrounding connective tissue had the appearance of aortic atheroma with lipid content. Frequently the surrounding tissue was vascular and showed mononuclear infiltrations. In one valve true cartilage and bone formation were noted. In other groups of hearts with known aortic endocarditis in various stages some were found in which calcareous nodules occurred which were identical with those in the above group and it could not be determined whether they had resulted from the inflammatory process or were merely coincidental.

In 1931 MARGOLIS, ZIELLESEN and BARNES¹⁴ reported a series of 42 examples of calcareous aortic valvular disease, 34 of which were in males. These were selected because they showed this condition at autopsy, without significant degrees of involvement of other valves. The majority of the patients were over 50 years old. In only three was a typical murmur of aortic stenosis found clinically. At autopsy, the aortic valves were characterized by varying amounts of calcium deposition with stiffening or distortion of the cusps. Some showed stenosis or insufficiency or both. The characteristic feature was the involvement primarily of the aortic ring, or frequently only of the commissures, and in the more marked cases, extension onto the cusps. All but one case showed coronary sclerosis and 14 showed scattered myocardial fibrosis. There were no infarcts. Microscopical examination revealed myocardial hypertrophy and slight increase in interstitial tissue. Cellular infiltrations were lacking in all but one case. The calcium masses were surrounded by old, practically acellular, fibrous tissue except those which extended to the surface. There the exposed side was covered by fibrin. Most of the valves were free from cellular infiltrations, but in five instances there were small collections of lymphocytes and endothelial leukocytes in the cusps near the calcareous deposits. Some of the capillaries supplying the cusps showed medial proliferation with thickening of their walls. As to etiology, these authors suggested rheumatic fever, but added that the distribution and gross and microscopical appearances were atypical. They suggested also an inflammatory process in the arterioles of the valve ring leading to obliteration and subsequent ischemia, or a generalized or selective atherosclerosis involving these arterioles and producing the same result. They found no evidence that the explanation lay in a healed bacterial endocarditis and mentioned the fact that syphilis is not a likely cause since it is not particularly prone to lead to calcification.

Still another group have favored the common infectious diseases of childhood or tuberculosis as the etiological factor.

In 1909 GALLAVARDIN¹⁰ wrote on a non-rheumatic aortic stenosis in young patients. He classified aortic stenosis as rheumatic, arterial (on a sclerotic basis), and congenital. To these three groups he added a fourth in which the etiology is obscure. This type is seen in young patients. There are indisputable physical signs and the lesion is purely, or at least predominantly, a stenosing one, due to fusion of the aortic cusps. It is perfectly tolerated for a long period of time. The author reported three cases of his own exemplifying this type of aortic lesion. Two of these were males, none had died when the paper was written. All had typical signs of aortic stenosis. He favored a slowly progressing chronic endocarditis during childhood and youth as the explanation and suggested tuberculosis or other infectious diseases of childhood as possible causes.

In 1921 GALLAVARDIN¹¹ wrote again on the same subject, presenting 10 additional cases. All of these were males (picked while examining young soldiers). All had typical physical signs of aortic stenosis except that in two the murmur was loudest at the left of the sternum. No autopsy reports were given.

In 1928 a case of non-rheumatic aortic stenosis in a young man of 24 was reported by ROUBIER and TOURNIAIRE¹⁸. There were definite clinical signs of aortic stenosis and no history of rheumatic fever or chorea. He had had cervical adenitis in childhood. Serological tests were negative for syphilis. Autopsy revealed a markedly enlarged heart (850 gm), a recent adhesive pericarditis, and a hard stenotic and insufficient aortic valve. The under surfaces of the cusps were covered by cartilage-hard tissue containing nodules of calcium and the cusps were interadherent. These authors thought the lesion to be on an inflammatory basis and discussed as possibilities an old endocarditis of the ordinary type and tuberculosis. They mentioned also the possibility of syphilis.

A fourth group have favored syphilis as the cause of this disease.

In 1903 ARMAND-DELILLE and J HEITZ¹ reported the case of a woman, aged 49 years, with a long history of gradually progressing symptoms of aortic stenosis. At autopsy a marked degree of calcification of the aortic valve with stenosis was found and, though they were unable to prove it, the authors thought syphilis was the cause.

In 1921 QUEYRAT and MOUQUIN¹⁰ described a child slightly less than six years of age on whom they had made a diagnosis of congenital syphilis on physical stigmata in spite of negative serological tests. There was no history of rheumatic fever, chorea or scarlet fever. Physical examination revealed an undoubted aortic stenosis. These authors made a diagnosis of congenital aortic stenosis. No autopsy report was given.

The remaining authors have considered rheumatic fever a probable cause of calcification of the aortic valve.

In 1901 BARIÉ² wrote a paper on acquired aortic stenosis and chronic aortitis in children. In reviewing the literature he was struck by the frequency of this diagnosis. He found eight cases ranging in age from two to fourteen years. Five of these came to autopsy, and calcification of the aortic valve was described in two. Aortic stenosis was found in six cases and was accompanied by aortic insufficiency in five. One of these six was not proved by autopsy. In one case only was there mention of alteration of the other valves, and this was in a child who developed mitral and aortic murmurs during an attack of rheumatic fever. Barié reported his own observation of a boy, aged 15 years, who had had scarlet fever at eight. This patient had clinical evidence of aortic stenosis. In discussing the subject he distinguished two types of aortic stenosis in children: one coming on during the course of acute articular rheumatism with the lesions on the ventricular surfaces of the aortic cusps at their free margins, the aortic stenosis of endocardial origin, the other, associated with a chronic preestablished aortitis. This, according to him, is the result of an arterial lesion which has extended to the valve cusps and is the more common. He concluded that in children it is more difficult to find the etiology than in adults in whom it can frequently be attributed to syphilis, typhoid fever, gout, lead poisoning, etc. In children, aortic stenosis is nearly always associated with other cardiopathy and is usually the sequel of chronic aortitis.

In 1930 DRAKE⁹ summarized the clinical aspects of sclerotic changes in the aortic valve. In his discussion he suggested that rheumatic fever or atherosclerosis might be the etiology though senile changes fail to explain all cases. He found the lesion most often in elderly males and remarked that often there were no accompanying valvular lesions. He often observed the absence of a systolic thrill in these cases.

and accounted for this on the basis of a weak myocardium. His cases had very little aortic insufficiency and consequently no abnormality in pulse pressure. They all showed a rather marked generalized atherosclerosis without marked involvement of the aorta.

In 1931 CHRISTIAN,^{5,6} in a paper entitled "Aortic Stenosis with Calcification of the Cusps," reported 21 cases ranging in age from 25 to over 60 years. Of these, 15 were males and all had no other valvular pathology. He found this lesion characterized clinically by its occurrence chiefly in males and relatively late in life, by its slow progression with cardiac decompensation appearing late, by the presence of a systolic thrill and harsh murmur over the aortic area, frequently accompanied by a softer blowing diastolic murmur, by considerable cardiac hypertrophy, by a decreased or normal pulse pressure, and by the absence of anything in the latter half of life to which the etiology might be attributed. At autopsy these hearts were characterized by increased weight, by marked narrowing of the aortic valve, and by thickened, often interadherent, cusps containing masses of calcium. In discussing etiology the author looked upon rheumatic fever as most likely since 11 of the 21 gave definite histories of this disease. Two others gave indefinite histories, and the remaining histories were probably unreliable because of the patients' condition or the lapse of time since the attack occurred. Against atherosclerosis with calcification as an explanation was the fact that most of the series showed little or no aortic atherosclerosis. He stated that the lesions in these cases bore no resemblance to syphilis of the aortic valve.

Also in 1931, CLAWSON⁷ discussed an analysis of 161 cases with nonsyphilitic aortic valve deformity, either occurring alone or associated with deformities of other valves. From this analysis he concluded that severe aortic valve deformity is usually of the calcareous nodular variety, that a severe grade of aortic stenosis is common in this deformity and should frequently be diagnosed clinically, that compensation and tolerance of the lesion is a more important factor in explaining its frequent incidence in elderly people than is its being an old-age disease and that the frequency of a rheumatic history in these patients suggests an infectious etiology. The gross and microscopic findings also indicate an inflammatory origin. He found no support for the metabolic theory of origin and said the term "arteriosclerotic valve deformity" is a misnomer.

The foregoing summary reviews some of the more important writings in the literature on this subject. It might be well to mention also some of the work on the blood vessels of the heart valves, since this may be of importance in the etiology of aortic valvular lesions of the type under consideration.

In 1917 BAYNE-JONES⁸ summarized the literature on this phase of cardiac anatomy and outlined a method of injection which he used to demonstrate blood vessels in the valves of human hearts. He found that in the semilunar valves the blood vessels arise from two sources: from the vasa vasorum of the aorta and pulmonary artery, and from the vessels of the auricular endocardium. From the former a few delicate vessels are given off at the line of attachment of the cusps to the wall of the artery and penetrate the valve for a short distance along its line of closure. Those from the latter source form a hedge-like plexus in the base of the cusp, and from this, delicate vessels pass upward for a distance of about one-half the width of the valve. He was unable to demonstrate vessels in the thin central portion of the valve cusps or in the noduli Arantii.

KUGEL,¹² in 1928, in an article entitled "Anatomical Studies on the Coronary Arteries and Their Branches," discussed the *arteria anastomotica auricularis magna*. He demonstrated this vessel by injection methods and described it as a large anasto-

motric artery linking the left and the right coronaries. It is constant in its occurrence, though subject to slight variations in its course. It supplies branches to the aortic cusp of the mitral valve and to the aortic valve cusps (when vessels are found in these sites), as well as to the commissures of the aortic valve and to the base of the aorta.

Later in 1928 RITTER, GROSS, and KUGEL¹⁷ presented a study of 14 cases out of 700 examined having *arteriae valvulares*, these 14 showing no evidence of any previous inflammatory process.

MATERIAL

For this study I have selected 52 cases showing aortic valve lesions. These have been divided into four groups, the first of which includes those showing sclerosis and calcification of the aortic valve with no obvious etiology. This group is further divided into two subgroups, one of which includes the cases showing no other essential valvular lesions and the other, those showing also other valvular changes. In group II are those cases in which there is definite pathological evidence of syphilis as an etiologic factor. Group III contains those cases with clinical or pathological evidence of rheumatic fever as the causative factor. In group IV there are a few cases showing active subacute bacterial or ulcerative aortic endocarditis without involvement of the other valves. Groups II, III, and IV have been selected for comparison with group I. Group I contains 29 cases, 10 of which show involvement of the aortic valve alone. In group II there are nine cases. Group III contains 11 while there are but three in group IV. The aortic valves in group IV show no calcification, these cases being included in order to obtain a comparison with active inflammatory aortic lesions.

In order to save space these various groups will be presented collectively with the incidence of various features given by number of cases. In the tables the same information is presented as percentages of the total number in the group to facilitate comparison.

GROUP I A UNDETERMINED ETIOLOGY, AORTIC VALVE ALONE AFFECTED

Of the 10 cases in group I showing no involvement of the other valves, seven were males. The average age was 52 years, the youngest patient being 30 and the oldest 84. Clinical records were available on only eight of the 10 and of these, six complained of undoubted cardiac symptoms. One had symptoms which might have been cardiac, but could be explained on the basis of the severe anemia which was also present. In one case the complaint was definitely non-cardiac. In the histories of this group of eight patients the following infections were recorded:

Infection	Number of Cases	Percentage of Group (8 cases)
Measles	4	50
Pneumonia	3	37½
Rheumatic fever	2 (1 questionable)	25
Scarlet fever	2	25
Diphtheria	1	12½
Typhoid fever	1	12½
Gonorrhea	1	12½
Influenza	1	12½
No infections	1	12½

In these eight records the physical examination showed cardiac enlargement in six. Seven had a systolic cardiac murmur and in four of these the murmur was best heard at the base. In one case there was an accompanying systolic thrill. One patient had a diastolic mitral murmur and one had no cardiac murmur. The average blood pressure of the six cases in which it was recorded was approximately 120 mm Hg systolic and 82 diastolic, the highest systolic pressure being 138. The lowest diastolic pressure was 10, in a patient *in extremis*. The three cases in which the result of the Kahn test was reported showed negative results. The cause of death as determined at autopsy was cardiac disease in four instances, in two, pernicious anemia, in three, carcinoma, and in one, pneumonia. Thus in six cases the cause of death can be considered non-cardiac.

At autopsy all of these hearts showed calcification of the aortic valve similar to that seen in figure 1. Nine showed cardiac enlargement. Seven had aortic stenosis of varying severity, and four of the group had an associated aortic insufficiency. Three showed no aortic stenosis or insufficiency. One heart showed adhesive pericarditis, while the others showed no pericardial abnormality save a soldier's spot in one and an increase in fluid in another.

Analysis of the microscopic studies of these ten hearts reveals no hypertrophy of the muscle fibers in four, slight in four, moderate in one and marked in one. In one case there was no atrophy of the muscle fibers, in eight atrophy was slight, and in one it was moderate in degree. None of the 10 showed hypoplastic fibers. Seven showed a slight degree of myocardial fibrosis, two showed a moderate degree and one a marked fibrosis. The distribution of this fibrosis was patchy in eight and diffuse in two. In no case was it perivascular. In four cases its character was fibroblastic, in five it was hyaline, one of these showing small fibroblastic areas. In one it was myxomatous with hyaline change in some areas.

Active cellular infiltrations were present in the myocardium to a slight degree in five of the cases. In two of these the infiltrations were perivascular. The remaining five hearts showed no infiltrations. In two, sections showed no interstitial tissue increase, six showed slight increase, one, a moderate, and one a marked increase. No Aschoff nodules were found in any of the group. Endocardial sclerosis, aside from that in the aortic area, was not present in two cases, only slight in three, moderate in three, and marked in two. Extension of the endocardial sclerosis into the myocardium was observed in varying degrees in six hearts. Five hearts revealed no fatty infiltration of the myocardium, two revealed a slight degree and three a moderate degree. Degenerative fatty infiltration was absent in one, slight in three and moderate in six. The small coronary vessels showed no sclerosis in seven cases, a slight degree in two and a moderate degree in one. The medium-sized coronary branches were negative in three, slightly sclerotic in five and moderately sclerotic in two. The large coronaries showed a slight degree of sclerosis in six, a moderate degree in three, one of which showed partial occlusion, and a marked degree in one.



FIG 1 Group I A Male, aged 30 Severe aortic stenosis with marked calcification of cusps and left ventricular hypertrophy

GROUP I B UNDETERMINED ETIOLOGY, OTHER VALVES ALSO ALTERED

The remaining 19 cases in group I are those which, in addition to aortic valve sclerosis, showed other valvular lesions. Of these, 12 were males. The average age for the group was 60 years, the youngest patient was 40 and the oldest was 98. The record on one of these patients was not available, so the percentages on the clinical findings are computed on a total of 18. Ten gave complaints which were definitely cardiac. The remainder gave

non-cardiac complaints The histories revealed the following infections in these patients

Infection	Number of Cases	Percentage of Group (18 cases)
Measles	8	44
Scarlet fever	6	34
Mumps	5	28
Whooping cough	4	22
Chicken pox	4	22
Rheumatic fever	3	17
Diphtheria	3	17
Smallpox	3	17
Quinsy	2	11
Tonsillitis or sore throat	2	11
Influenza	2	11
Typhoid fever	2	11
Malaria	1	6
Pneumonia	1	6
Hard chancre	1	6
"Usual childhood diseases"	2	11
No infections	5	28

Physical examination revealed cardiac enlargement in 10 of the 18. A systolic murmur was heard in 14, in seven of these it was loudest at the base and in the other seven it was best heard at the apex. Five had a diastolic murmur. Seven had a greater or lesser degree of sclerosis of the peripheral vessels. The average blood pressure of the group was 153 mm Hg systolic and 94 diastolic, the highest systolic being 224, and the highest pulse pressure 104. In the 12 cases on which the Wassermann or Kahn test was done there were negative reports.

The causes of death in these 19 cases, based on the autopsy findings, were as follows: six, malignancy (five carcinomas, one hypernephroma), five, arteriosclerosis (including cardiopathia arteriosclerotica), four, mitral or aortic valvular disease, or both, one, hemiplegia, one, pneumonia, one, pulmonary tuberculosis, and one, pansinusitis.

Examination of the hearts at autopsy revealed definite cardiac enlargement in 12, the heaviest heart weighing 770 gm, five showed an old patchy epicarditis. Twelve showed no stenosis of either the mitral or aortic valve. Seven showed valvular stenosis as follows: mitral valve alone, four (one with insufficiency also), aortic valve alone, one, and both valves, two.

The microscopic findings are summed up as follows: hypertrophy of muscle fibers was absent in six, slight in 10, and moderate in three. Atrophy was absent in four, slight in six, and moderate in nine. Hypoplasia of the muscle fibers was absent in 18 and present to a moderate degree in one. The amount of fibrosis of the heart wall was considered slight in nine cases and moderate in 10. This connective tissue had a patchy distribution in 12 cases, in one of which it was perivascular in some areas. It was diffuse in two cases and especially perivascular in five. Its character was predominantly fibroblastic in seven cases in one of which it was hyaline in areas. It was predominantly hyaline in 12 cases, in three of which there were fibroblastic areas, one with myxomatous regions.

Active cellular infiltrations were not found in 11 of these cases, they were considered slight in seven and moderate in one. In four of these they were perivascular in distribution. Increased stroma was absent in one case, slight in eight and moderate in 10. No Aschoff nodules were found in these 19 cases. Endocardial sclerosis other than valvular was not found in five cases, was only slight in six, moderate in seven and marked in one. In 16 it extended into the myocardium in varying degrees.

Fatty infiltration was absent in 12 cases, slight in four and moderate in three. Degenerative fatty infiltration was absent in two cases, slight in nine, moderate in five and marked in three. The small coronary vessels showed no sclerosis in 14 cases, the medium-sized ones, none in nine cases, and the large ones, none in two cases. A slight degree of sclerosis was observed in the small ones in five cases, in the medium-sized ones in five cases, and in the large ones in 10 cases. A moderate degree was found in the medium-sized vessels in five cases and in the large ones in one case. Marked coronary sclerosis was observed in six cases, in all of which it was present only in the larger branches.

GROUP II ETIOLOGY DETERMINED TO BE SYPHILIS

In group II there are six males and three females. The average age of the group was approximately 49 years, the oldest individual being 68 and the youngest, 18. In one patient the clinical record was not available and in another the complaint was not obtained because the patient was in a stuporous condition on admission. Of the seven on whom complaints were recorded three were non-cardiac and four, cardiac. The eight histories reviewed revealed the following infections:

Infection	Number of Cases	Percentage of Group (8 cases)
Influenza	2	25
Hard chancre	2	25
Gonorrhea	2	25
Measles	1	12½
Scarlet fever	1	12½
Whooping cough	1	12½
Quinsy	1	12½
Tonsillitis or sore throat	1	12½
Typhoid fever	1	12½
Malaria	1	12½
Pneumonia	1	12½
Rheumatic fever	1	12½
Running ear	1	12½
"Usual childhood diseases"	2	25
No infections	2	25

Physical examination revealed cardiac enlargement in seven of the eight whose records were available. In one of these it was recorded as slight, in the other case there was no enlargement. Systolic murmurs were heard in six cases, in two of which the maximum intensity was at the base. In two cases a diastolic murmur was heard at the apex and in one of these there was an accompanying thrill. A presystolic murmur at the apex was noted

in one case In three cases diastolic murmurs were heard at the base Results of the Kahn test were reported on two, one, negative, and the other, two plus The average blood pressure in the five cases of the group in which it was recorded was 133 mm Hg systolic and 85 diastolic, the highest systolic pressure being 160 and the highest pulse pressure being 68

The causes of death as determined at autopsy were as follows carcinoma of prostate in one instance, syphilitic heart disease in two, syphilis of the aorta in three, in one of which there was aortic valvular insufficiency, in another an accompanying syphilitic involvement of the myocardium and aortic valve, and in the third an aortic aneurysm One death was due to aortic stenosis and insufficiency with a generalized atherosclerosis, another was a thymico-lymphatic death, and another was due to rheumatic heart disease In this last case it was determined microscopically that syphilis also was a factor

The hearts in these cases were found enlarged at autopsy in eight instances, the largest one weighing 1350 gm There was an area of adhesive pericarditis in one case, soldier's spots in three and hydropericardium in one Bilateral ventricular mural thrombi were found in one Both the aortic and mitral valves showed sclerosis and calcification in three cases and in one of these there was thickening of the tricuspid flaps also In six cases the valvular involvement, except for relative insufficiency, was limited to the aortic valve There was aortic stenosis in three and in two of these there was an associated insufficiency Aortic insufficiency without stenosis occurred once and one case showed mitral stenosis and insufficiency Four hearts showed no valvular stenosis or insufficiency

Analysis of the microscopic studies on this group reveals no hypertrophy of the muscle fibers in four cases, slight hypertrophy in three, and moderate in two Atrophy of the muscle fibers was absent in two, slight in four, and moderate in three Hypoplasia was absent in all nine cases The degree of fibrosis of the myocardium was slight in two cases, moderate in six, and marked in one This connective tissue was distributed diffusely in eight cases (two showing a patchy distribution in areas), and had a patchy distribution in one case It was hyaline in five cases (two showing fibroblastic areas), myxomatous with fibroblastic areas in one, and fibroblastic in three (one showing hyaline areas) Active cellular infiltrations were found to a slight degree in three cases, to a moderate degree in five and to a marked degree in one These were perivascular in distribution in five cases A slight degree of increase of stroma was observed in two cases and a moderate degree in seven No Aschoff nodules were found in any of this group

All nine cases showed endocardial sclerosis in addition to that on the valves In three it was slight in amount, in five it was moderate, and in one, marked In two cases there was no extension into the myocardium The others showed varying degrees of extension Fatty infiltration of the myocardium was absent in five cases, slight in three and marked in one Degenerative fatty infiltration was slight in two cases, moderate in four and

ment without involvement also of some of the other valves. The aortic valve lesions varied from slight sclerosis to marked calcification with inter-adherent cusps. There was no aortic stenosis in the group.

Summary of the microscopic findings in this group shows absence of muscle hypertrophy in three hearts, slight hypertrophy in five and moderate hypertrophy in three. Atrophy of the muscle fibers was absent in two, slight in four and moderate in five. Hypoplasia was not observed in any. Fibrosis of the myocardium was slight in three cases, moderate in six and marked in two. The distribution of the fibrosis was predominantly perivascular in seven, four of these showing diffuse areas and two showing areas in which the distribution was patchy. Four showed a predominantly diffuse distribution, two having areas with a perivascular and three, a patchy distribution. The connective tissue was hyaline in six hearts, three of these showing fibroblastic areas, fibroblastic in four, two of these showing hyaline areas, and myxomatous in one, this one showing also some fibroblastic areas. Active inflammatory infiltrations were not found in three cases. They were slight in five, moderate in two and marked in one. In seven the infiltrations had a perivascular distribution. An increase of stroma was observed in all 11 cases, in three it was slight in amount, in six it was moderate and in two it was marked. Aschoff nodules were not found in seven cases, in one case only a few were found, and in three they were moderate in number. Endocardial sclerosis, other than valvular, was slight in amount in three cases, moderate in seven and marked in one. It extended into the myocardium slightly in five and moderately in six.

Fatty infiltration of the myocardium was absent in two cases, slight in six, moderate in two and marked in one. Degenerative fatty infiltration was slight in three cases, moderate in seven and marked in one. The coronary vessels were relatively free from sclerosis. The small and medium-sized branches showed none in nine cases and the large ones, none in four cases. The small branches showed a slight degree of sclerosis in one and a moderate degree in one, while the medium-sized branches showed only a slight degree in two cases. The large vessels showed a slight degree in five and a moderate degree in two. In one case one of the large vessels was partially occluded by a sclerotic plaque.

GROUP IV ACTIVE VEGETATIVE AND ULCERATIVE AORTIC VALVULITIS

The three cases in group IV are studied merely for comparison in the hope of discovering the etiology of calcification of the aortic valve. Two were males and the average age was 34 years, the youngest being 26 and the oldest, 47. One of these patients entered the hospital complaining of chills and fever and swelling of the feet and ankles. The other two had definite cardiac complaints, one being *in extremis*. The infections that these patients remembered having had are given in the following table.

Infections	Number of Cases	Percentage of Group (3 cases)
Measles	2	66 $\frac{2}{3}$
Whooping cough	2	66 $\frac{2}{3}$
Chicken pox	1	33 $\frac{1}{3}$
Mumps	1	33 $\frac{1}{3}$
Sore throat	1	33 $\frac{1}{3}$
Quinsy	1	33 $\frac{1}{3}$
Scarlet fever	1	33 $\frac{1}{3}$
Diphtheria	1	33 $\frac{1}{3}$

Physical examination revealed cardiac enlargement in two, and systolic and diastolic murmurs at both the apex and base in all three cases. The result of the Wassermann test, reported on one record, was negative. Blood culture was positive for *Streptococcus viridans* in one case and not reported on the others. The average blood pressure was 116 mm Hg systolic and 51 diastolic in the two patients for whom it was recorded. One of these had a pulse pressure of 80.

The causes of death as determined at autopsy were subacute ulcerative aortic endocarditis, vegetative aortic endocarditis, and subacute vegetative and ulcerative aortic endocarditis with mycotic aneurysm. Cardiac enlargement was found in two of the three at autopsy. Two had a patchy adhesive pericarditis and one an hydropericardium. The aortic and mitral valve lesions varied from vegetative to ulcerative in type, the aortic valve in one showing a mycotic aneurysm. One aortic valve was bicuspid. Postmortem blood culture was positive for *Streptococcus viridans* in one instance (not the case with the positive antemortem culture).

Summary of the microscopic findings in group IV reveals no hypertrophy of the muscle fibers in one case and moderate hypertrophy in two. Atrophy was absent in one, slight in one and moderate in one, while hypoplasia was absent in all three. Myocardial fibrosis was slight in amount in two cases and moderate in amount in one. Its distribution was diffuse in one, patchy in one and perivascular in one. It was fibroblastic in all three. Active inflammatory infiltrations of the myocardium were found in one of the three cases where they were moderate in extent. In this case they were not perivascular in distribution. Increased stroma was considered slight in two cases and moderate in one. Aschoff nodules were found in none of these cases.

Endocardial sclerosis was absent in one case, slight in amount in one and moderate in one. In two it did not extend into the myocardium and in one showed only slight extension. Fatty infiltration of the myocardium was slight in all three cases. Degenerative fatty infiltration was moderate in all. Sclerosis of the small, medium-sized, and large coronary vessels was absent in all three cases.

COMPARATIVE SUMMARY

To facilitate the comparison of the foregoing groups of cases tables are given. (See tables 1, 2 and 3.) In addition a brief comparative summary seems necessary. Sclerosis and calcification of the aortic valve seem to

TABLE I

Percentage Distribution of Clinical Findings in Four Groups of Aortic Valvular Lesions

Group	Sex		Average Age	Complaints		History of Infections						
	Male	Female		Cardiac	Non-Cardiac	Measles	Scarlet Fever	Rheumatic Fever	Diphtheria	Tonsillitis	Gonorrhea	Syphilis
I { A	70	30	55	75	25	50	25	12½	12½	0	12½	0
	B	63	37	60	55	44	34	17	17	11	0	6
II	66½	33½	49	57	43	12½	12½	12½	0	12½	25	25
III	55	45	26	100	0	55	9	55	18	36	9	0
IV	66½	33½	34	66½	33½	66½	33½	0	33½	33½	0	0

TABLE I (Continued)

Group	Physical Examination						Cause of Death		
	Cardiac Enlargement	Systolic Murmur	Diastolic Murmur	Systolic Thrill	Diastolic Thrill	Average Blood Pressure	Pneumonia	Malignancy	Cardiac Disease
I { A	75	87½	12½	12½	0	120/82	10	30	40 *
	B	55	78	28	0	153/94	5	30	47 †
II	87½	75	75	0	12½	133/85	0	11	78 ‡
III	100	82	91	9	27	141/38	0	0	100
IV	66½	100	100	0	0	116/51	0	0	100

* The other two died from pernicious anemia

† The remaining 18 per cent died from hemiplegia, pulmonary tuberculosis and pansinusitis

‡ The other was considered a thymicolymphatic death

occur slightly more frequently in the male than in the female. The average age of these groups varies somewhat, that of the group of rheumatic fever cases being the lowest, the active endocarditis group next in the age scale, the syphilitic group next and the group of unknown etiology highest. In a rough way then, these four groups can be separated according to the average age at which death occurred.

The complaints of the patients upon entering the hospital indicate that they sought medical attention primarily for heart disease, more often than for remote diseases. Study of the incidence of the various infections in

these groups reveals nothing by which any one of them can be characterized. Measles occurred in about one-half of each group except group II, in which there was an incidence of but 12.5 per cent. The incidence of scarlet fever varied from about one-eighth to one-third, the lowest being in group III, the rheumatic fever group, and the highest being in the second division of group I. This disease has been blamed for the occurrence of aortic endocardial sclerosis, but its incidence in our series is not sufficiently high to lend much weight to this opinion. The incidence of a history of rheumatic fever varied from about one-eighth to one-fourth except in the rheumatic fever group where it was slightly over one-half. It was approximately the same in the syphilitic group as in the unknown group, so these figures do not point conclusively to rheumatic fever as the etiology in group I. The incidence of

TABLE II

Percentage Distribution of Gross Pathological Cardiac Findings in Four Groups of Aortic Valvular Lesions

Group	Cardiac En- largement	Aortic Valve Calcification	Aortic Stenosis	Aortic In- sufficiency	Mitral Valve Calcification	Mitral Stenosis	Mitral In- sufficiency	Pericarditis
I { A	90	100	70	40	0	0	0	10
	B	63	100	16	0	47	32	5
II	89	100	33	33	33	11	11	44
III	100	9	0	0	45	45	27	45
IV	66 $\frac{2}{3}$	66 $\frac{2}{3}$	66 $\frac{2}{3}$	33 $\frac{1}{3}$	0	0	0	66 $\frac{2}{3}$

diphtheria is likewise as high outside of group I as within it except for group II in which no history of diphtheria was obtained. Tonsillitis, or sore throat of frequent occurrence, was higher in its incidence outside of than inside of group I. History of gonorrhea and syphilis did not occur more frequently among the cases in group I than in the other groups in spite of the known fact that gonorrheal endocarditis frequently involves the aortic valve alone. Typhoid fever, which has also been cited as a possible etiologic factor, occurred in about one-eighth of each of the groups except in group IV where it did not occur at all. It should be remembered, also, that the members of our group I, having the highest average age, have a better chance to have had these infections, and should, therefore, have a higher incidence of them. Another point to be considered is that the older patients may have forgotten the infections of earlier life.

On physical examination a majority of all the groups showed cardiac enlargement, and a systolic murmur was heard in over three-fourths of every group. It is surprising that such a high proportion showed clinical signs of

valvular lesions when we consider that a much lower percentage actually showed valvular stenosis or insufficiency at autopsy. The importance of the systolic thrill in making a clinical diagnosis of calcareous aortic valvular disease with stenosis has been emphasized in the literature. In this series of patients including all four groups, it was recorded only twice, aortic stenosis being found at autopsy 16 times. In groups II, III and IV a diastolic thrill was observed five times, mitral stenosis being found at autopsy six times in these groups. The average blood pressures of the several groups were not

TABLE III

Percentage Distribution of Microscopic Findings in Four Groups of Aortic Valvular Lesions

Group	Hypertrophy				Atrophy				Fibrosis				Distribution of Fibrosis			Character of Fibrosis		
	Absent	Slight	Moderate	Marked	Absent	Slight	Moderate	Marked	Absent	Slight	Moderate	Marked	Patchy	Diffuse	Perivascular	Fibroblastic	Hyaline	Myxomatous
I { A	40	40	10	10	10	80	10	0	0	70	20	10	80	20	0	40	50	10
	B	32	53	15	0	21	32	47	0	0	47	53	0	64	10	26	37	63
II	45	33	22	0	22	45	33	0	0	22	67	11	11	89	0	33	56	11
III	27	46	27	0	18	36	46	0	0	27	55	18	0	36	64	36	55	9
IV	33½	0	66⅔	0	33½	33½	33½	0	0	66⅔	33½	0	33½	33½	33½	100	0	0

TABLE III (Continued)

Group	Active Infiltrations				Distribution of Infiltrations		Increased Stroma				Aschoff Nodules		Endocardial Sclerosis				Extension into Myocardium of Endocardial Sclerosis		
	Absent	Slight	Moderate	Marked	Diffuse	Perivascular	Absent	Slight	Moderate	Marked	Absent	Present	Absent	Slight	Moderate	Marked	Absent	Present	
I {	A	50	50	0	0	80	20	20	60	10	10	100	0	20	30	30	20	40	60
	B	58	37	5	0	79	21	5	42	53	0	100	0	26	32	37	5	16	84
II	0	33	56	11	44	56	0	22	78	0	100	0	0	33	56	11	22	78	
III	27	46	18	9	33	67	0	27	55	18	64	36	0	27	64	9	0	100	
IV	66½	0	33½	0	100	0	0	66½	33½	0	100	0	33½	33½	33½	0	66½	33½	

TABLE III (Continued)

Group	Fatty Infiltration				Degenerative Fatty Infiltration				Coronary Atherosclerosis												
									Small Branches				Medium-sized Branches				Large Branches				
	Absent	Slight	Moderate	Marked	Absent	Slight	Moderate	Marked	Absent	Slight	Moderate	Marked	Absent	Slight	Moderate	Marked	Absent	Slight	Moderate	Marked	
I {	A	50	20	30	0	10	30	60	0	70	20	10	0	30	50	20	0	0	60	30	10
	B	63	21	16	0	10	48	26	16	74	26	0	0	48	26	26	0	10	53	5	32
II		56	33	0	11	0	22	45	33	56	22	0	22	67	22	11	0	33	45	0	22
III		18	55	18	9	0	27	64	9	82	9	9	0	82	18	0	0	36	46	18	0
IV		0	100	0	0	0	0	100	0	100	0	0	0	100	0	0	0	100	0	0	0

at wide variance when the average ages of the groups are considered. The highest systolic pressure in the entire series was 224 in a woman of 63 with a marked generalized atherosclerosis.

The causes of death were predominantly cardiac in all except group I where more frequently the cause was remote. Autopsy revealed a slightly higher percentage of cardiac enlargement in group I than was determined clinically but in the other groups the agreement was very close. The high proportion of these cases having cardiac enlargement is in accordance with the findings of other investigators on this subject. The fact that calcification of the aortic valve was not found in 100 per cent of groups III and IV has been explained before. The occurrence of aortic stenosis was considerably more frequent in group I, especially in subdivision A. This may be accounted for partly on the basis of age, the sclerosing process having had more time to produce stenosis in the older patients. Aortic insufficiency as found at autopsy was relatively infrequent except in the syphilitic group where it occurred as frequently as did stenosis. Calcification of the mitral valve, absent from group I A by selection, is much less common than calcification of the aortic valve in the remainder of the series except in the rheumatic fever group where it is five times more common. Naturally the occurrence of mitral stenosis and insufficiency bears a similar relation to aortic stenosis and insufficiency. The occurrence of pericarditis in any form was much less common in group I A, being more prevalent in those groups in which there were more active lesions of an inflammatory nature and especially in the rheumatic fever group.

Comparison of the microscopic findings in the various groups reveals strikingly little variation in the amount of hypertrophy of the myocardium observed. There is a rough proportion between this and the degree of aortic

stenosis or the severity and chronicity of the cardiac disease. Likewise atrophy of the myocardium is not distinctive in any particular group but seems to be proportionate to the average age of the group. Myocardial fibrosis showed the highest incidence in the syphilitic group and next highest in the rheumatic fever group. It was present to a marked degree in only one case of group I and this was a patient with arteriosclerotic heart disease. The fibrosis had a patchy distribution in the majority of the cases in both divisions of group I. In the syphilitic group its distribution was predominantly diffuse, while in the rheumatic and ulcerative groups the majority showed perivascular distribution. The character of the fibrosis was predominantly hyaline in every group except number IV, where it was fibroblastic.

Active infiltrations in the myocardium were not outstanding in group I, though they were considered a little more prominent in that part of the group showing involvement of other than the aortic valve. In the other groups active infiltrations were present in the majority of the cases except in group IV. These infiltrations showed a predominantly diffuse distribution in group I, a slight tendency to perivascular distribution in the syphilitic group and a fairly marked tendency in this direction in the rheumatic group. Increased stroma was found to a considerable extent in every group but was most marked in the rheumatic group. The syphilitic group was next in order. Aschoff nodules were found only in group III, and even here in a relatively low percentage of the cases.

Sclerosis of the endocardium was found to be fairly constant all through the series, being most marked in group I A, and in the great majority of cases in which it occurred there was extension into the myocardium. Fatty infiltration of the myocardium was absent in half or more of the cases in groups I and II, being a more prominent feature of the rheumatic and ulcerative groups in spite of the lower age figures in these groups. Degenerative fatty infiltration, on the other hand, was present in nearly every case of the entire series. It was most marked in groups II, III, and IV.

Atherosclerosis of the small coronary arterial branches was absent in nearly three-fourths of the cases in group I. A smaller number of the medium-sized branches, however, showed negative findings, over half of the group presenting atherosclerosis either to a slight or a moderate degree, but none to a marked degree. The larger branches in group I showed a fairly marked sclerosis, more than did any other group. In group II the small branches were free from sclerosis in slightly over half of the cases, but half of those showing sclerosis showed it to a marked degree. In this group, also, the medium-sized branches were relatively free from sclerosis and the large branches showed a much less degree than did those of group I. In groups III and IV sclerosis of the small and medium-sized branches was rare indeed. The large branches in group III showed a slight degree of sclerosis while those of group IV showed none.

DISCUSSION AND CONCLUSIONS

Consideration of the ages of the groups of cases studied indicates that those with sclerosis of the aortic valve of the type whose etiology is not clear live longer than those of known syphilitic or rheumatic origin. This finding cannot be used to rule out rheumatic fever or syphilis in the older group, however, since this group may have had stronger constitutions, or have been less severely attacked by the causative disease, or attacked later in life.

The possibility that some of the frequent infections found in the past

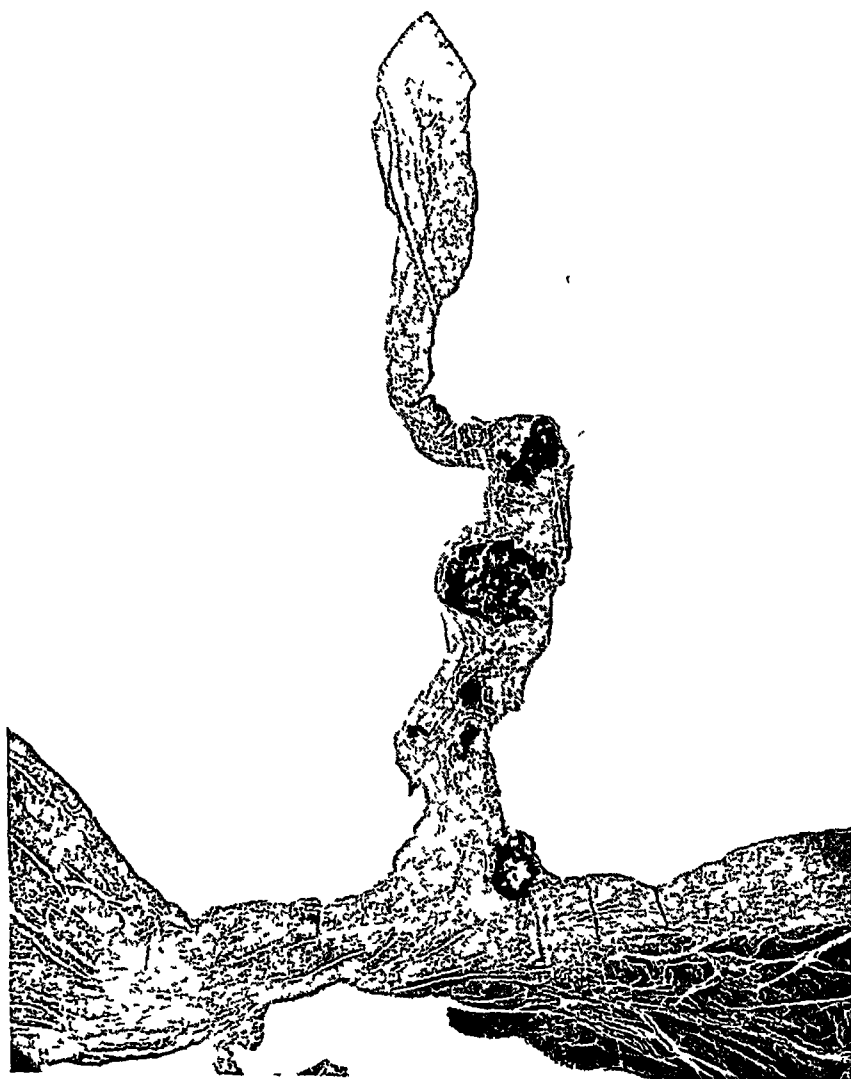


FIG 2 Group I A Female, aged 52 Aortic valve cusp showing calcareous nodules
Patient had a severe aortic stenosis ($\times 7$)

histories could be etiologic factors in this type of stenosis of the aortic valve seems unlikely since there are none which specifically characterize our unknown group. While too much stress should not be placed on histories, it is significant that rheumatic fever was mentioned by but 12.5 per cent of the members of this group.

The clinical findings in these groups of patients need not be discussed further except to say that, unless there is a fairly marked aortic stenosis present, sclerosis of the aortic valve with calcification may not be recognized by the clinician, unless perchance it be detected by the roentgenologist. The blood pressures in this series of patients were not distinctive in any one group.



FIG 3 Greater magnification of calcareous nodule seen in figure 2 at base of cusp
Note absence of evidence of inflammatory reaction ($\times 45$)

When the microscopical studies are considered and group I A compared with the other groups, there is noted strikingly little evidence of inflammatory processes in group I A (figures 2, 3 and 4). Pericarditis was less common in this group, myocardial fibrosis was less prevalent and in the case where it did occur to a marked degree could be accounted for on the basis of arteriosclerosis. The distribution of the fibrosis found in group I A was more that of arteriosclerotic cardiopathy than of any form of infectious

myocarditis of which we have knowledge. Active infiltrations of the myocardium were not a characteristic feature of group I. They were slightly more noticeable in I B than in I A, however, and this fact, together with the slightly greater incidence of fibrosis in I B, is the only point of difference observed to indicate that such a separation is justified. Where active infiltrations occurred in group I they were usually diffuse in distribution which is against rheumatic myocarditis in its active stage. The cellular infiltra-



FIG. 4 Greater magnification of one of the calcareous nodules seen in figure 2
Note absence of evidence of inflammatory reaction ($\times 60$)

tions about the calcium deposits in the aortic valve were similar to those seen in the aorta about calcareous deposits (figure 5). Even though increased stroma was fairly prevalent in group I it was less so than in the other groups. The absence of Aschoff nodules from group I is excellent evidence against rheumatic fever as the etiology. To be sure, they were not found in all of the cases in the rheumatic group, but examination of many more sections

from the cases where they were not demonstrated would very likely have raised the percentage considerably. On the other hand, group I contains many more cases, and if the etiology were rheumatic fever in this group some of these hearts must surely have contained these pathognomonic nodules.

Endocardial sclerosis, aside from that in the aortic area of these hearts, was considered. It was found most marked in group I where there was



FIG 5 Group I B Male, aged 66 Calcareous nodule at base of aortic cusp showing slight cellular infiltration nearby ($\times 100$)

least evidence of inflammation in the myocardium and most evidence of atherosclerosis with involvement of the coronary vessels.

From the evidence gathered in this study then, one must conclude that sclerosis of the aortic valve, with varying degrees of calcification and stenosis, in those cases without obvious etiology, such as syphilis or rheumatic fever, is not on an infectious basis but rather on the same basis as atherosclerosis.

It is not unreasonable to draw an analogy between the aortic valve and the aorta. In the latter we frequently find extensive calcium deposits and no evidence of any foregoing infectious process. We explain this as a "metabolic" disturbance and if we find cellular infiltrations about the calcareous nodules we consider them secondary. If, on the other hand, there is evidence of an old syphilitic aortitis we may make a diagnosis of aortic atherosclerosis on a syphilitic basis. Thus also with the aortic valve, it may be concluded that the final picture of aortic endocardial sclerosis with calcification and stenosis can be produced either by a chronic inflammatory process or a metabolic disturbance. The evidence in this series, however, indicates that in those cases having obscure etiology and showing other characteristics in common with the group presented by Christian,^{5, 6} the condition develops upon a noninfectious basis.

SUMMARY

1 Fifty-two cases were selected from 4,000 consecutive autopsies for the purpose of studying calcareous aortic valvular disease.

2 These cases were divided into four main groups, the first having two subdivisions.

Group I A Ten cases showing calcareous aortic valvular disease with varying degrees of stenosis, undetermined etiology and no other important valvular alterations.

Group I B Nineteen cases showing calcareous aortic valvular disease with significant changes in other valves.

Group II Nine cases showing calcareous aortic valvular disease with known syphilitic etiology.

Group III Eleven cases showing lesions of the aortic valve of known rheumatic fever origin.

Group IV Three cases showing active aortic valvulitis of nonsyphilitic and nonrheumatic origin.

3 The clinical and pathological findings in these groups of patients have been presented, analyzed and compared.

4 Certain conclusions have been drawn from this study.

a There is no proof that the etiology of aortic stenosis of the type seen in group I A lies among the infectious diseases, since none of these diseases specifically characterizes this group.

b Microscopical studies indicate that stenosing calcareous aortic valvular disease in those cases without obvious cause, such as syphilis or rheumatic fever, is usually on a noninflammatory basis.

c Unless the stenosis be fairly well marked, calcareous aortic valvular disease may not be diagnosed on physical signs without the aid of the roentgenogram.

d The end result of a chronic aortic valvulitis may not be distinguishable from that of the noninflammatory calcareous lesion.

REFERENCES

- 1 ARMAND-DELILLE, P, and HEITZ, J Retrecissement aortique datant d'une syphilis juvenile Tolerance remarquable malgre l'etrottesse extreme de l'orifice, Soc Anat, 1903, v, 139-142
- 2 BARIE, E Le retrecissement aortique acquis et l'aortite chronique dans l'enfance, Soc Med des Hôp, 1901, iii, 872-880
- 3 BAYNE-JONES, S The blood vessels of the heart valves, Am Jr Anat, 1917, xxi, 449-462
- 4 CABOT, R C Endocarditis of aortic valve with calcification, stenosis, and insufficiency, Boston Med and Surg Jr, 1926, cxcv, 952-957
- 5 CHRISTIAN, H A Aortic stenosis with calcification of the cusps, Jr Am Med Assoc, 1931, clviii, 158-161
- 6 CHRISTIAN, H A Aortic stenosis with calcification, Internat Clin, 1931, iii, 51-54
- 7 CLAWSON, B J Nonsyphilitic aortic valve deformity, Arch Path, 1931, xii, 889-899
- 8 CLAWSON, B J, BELL, E T, and HARTZELL, T B Valvular diseases of the heart, Am Jr Path, 1926, ii, 193-234
- 9 DRAKE, C B The clinical aspects of sclerotic changes in the aortic valve, Minn Med, 1930, xiii, 628-631
- 10 GALLAVARDIN, L Du retrecissement aortique non rhumatismal des jeunes sujets, et de son analogie avec le retrecissement mitral de duroziez, Lyon Med, 1909, cxii, 189-206
- 11 GALLAVARDIN, L Retrecissement aortique non rhumatismal des jeunes sujets, Presse med, 1921, xxix, 224-225
- 12 KUGEL, M A Anatomical studies on the coronary arteries and their branches I Arteria anastomotica auricularis magna, Am Heart Jr, 1928, iii, 260-270
- 13 LECLERC, M F Deux cas de rétrécissements aortiques avec maximum du souffle à gauche du sternum, Lyon Med, 1905, cv, 941-945
- 14 MARGOLIS, H M, ZIELLESFN, F O, and BARNES, A R Calcareous aortic valvular disease, Am Heart Jr, 1931, vi, 349-374
- 15 MONCKEBERG, J G Der normale histologische Bau und die Sklerose der Aortenklappen, Arch f path Anat, 1904, clxxvi, 472-514
- 16 QUEYRAT, L, and MOUQUIN Retrecissement aortique congenital, probablement d'origine syphilitique hereditaire, chez un enfant de cinq ans, Soc Med des Hôp, 1921, xlv, 1152-1155
- 17 RITTER, S A, GROSS, L, and KUGEL, M A Blood vessels in the valves of normal human hearts, Am Heart Jr, 1928, iii, 433-446
- 18 ROUBIER, CH, and TOURNIAIRE, A Un cas de retrecissement aortique non rhumatismal chez un jeune sujet, Lyon Med, 1928, cxlii, 553-557
- 19 TUOHY, E L, and ECKMAN, P F Aortic stenosis with calcareous nodules in the aortic valves, Minn Med, 1931, xiv, 289-295

THE TREATMENT OF CHRONIC INTRACTABLE ASTHMA WITH POLLEN EXTRACTS¹

By GEORGE L. WALDBOTT, M D , F A C P , *Detroit, Michigan*

Most clinicians are in agreement that pollen is the most important cause of asthma (Duke,¹ Walzer,² Vaughan³) While there are many ardent advocates of measures to combat factors other than pollen—especially food, bacterial infections, house dust, and physical allergy—relatively little stress has been laid on the treatment of chronic asthma due to pollen

The obvious reason for this is, of course, the difficulty of recognizing the apparent paradox that in a patient who has been wheezing continuously throughout many years, the asthmatic condition may have originated from seasonal pollen asthma or pollen hay fever Furthermore, in the chronic asthmatic, skin tests are frequently of limited value, a fact which adds greatly to the diagnostic difficulties Negative tests are often encountered in the face of definite sensitivity (Peshkin⁴) On the other hand, if in this type of asthmatic treatment is instituted, frequently such marked sensitivity may be encountered that even the smallest dose of pollen extract produces a great aggravation of the symptoms and therefore discourages the patient and the doctor from further pollen injections

An additional reason for the lack of enthusiasm concerning this treatment is this whereas there have been many effective measures, such as the elimination of foods and of epidermals, etc., which were available for combating asthma due to substances other than pollen, until recent years pollen treatment had not been sufficiently perfected to be successful in the treatment of the more severe types of hay fever and particularly of asthma Three distinct advances in regard to this treatment can be recorded as being of relatively recent date first, the surveying and charting of the air content of pollen in various cities, initiated and fostered by O C Durham, secondly the realization of the fact that some patients need considerably larger doses than those formerly given, thirdly, the introduction of perennial pollen treatment by A Brown,⁵ and its further elaboration by Figley,⁶ Vaughan,⁷ and others

RÔLE OF POLLEN IN PERENNIAL ASTHMA

In looking over the skin test records of 121 consecutive patients with chronic asthma of the perennial type, it was found that there were more positive skin reactions to pollen than to any other group of allergens (Table 1) Among the 121 patients, in 65 the approximate date of the first onset of asthma could be definitely determined from the history The analysis showed that in 63 per cent the first attacks started between August 15 and September 30, the ragweed season, in 20 per cent, during June and July

* Read at the Montreal Meeting of the American College of Physicians, February 9, 1933

TABLE I

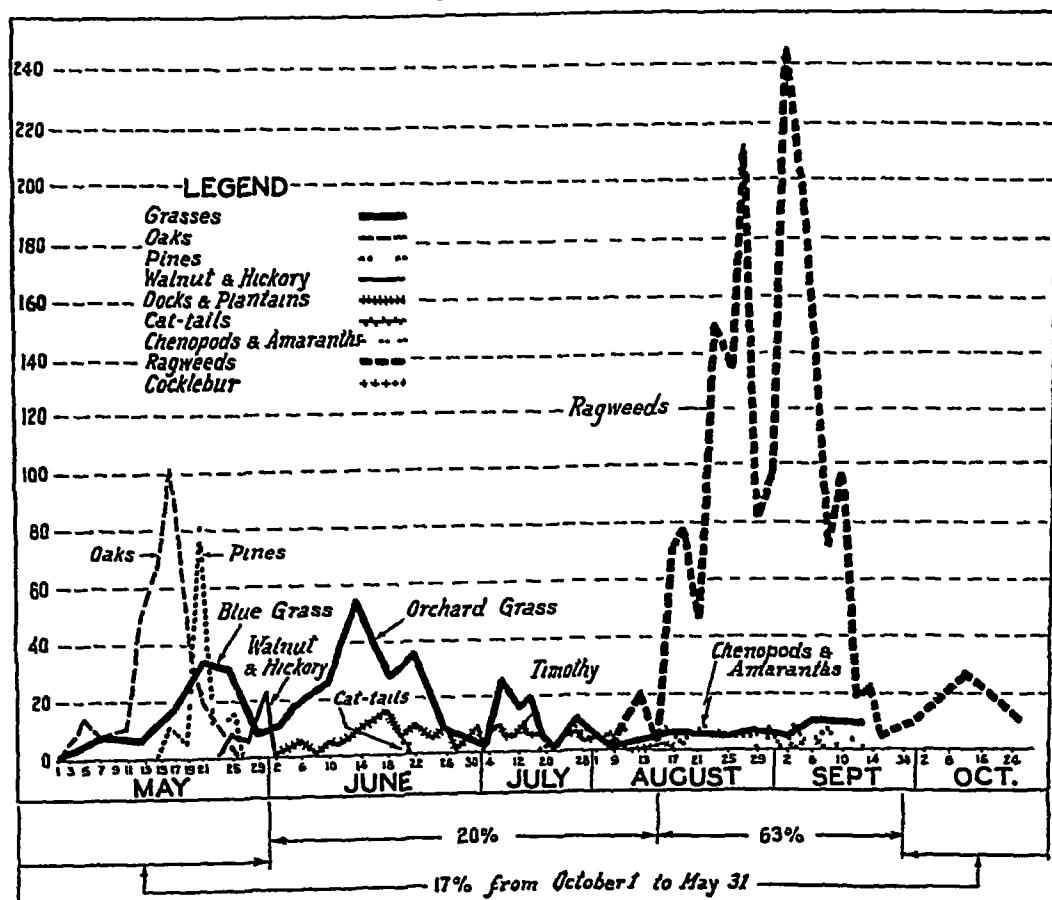
Comparison of Positive * Pollen Reactions with Those of Epidermals and Foods in 121 Cases

	Epidermals	Food	Pollen
Positive skin tests (exclusive of bacteria, fungi, dusts, and "incidentals")	483	1699	1330
Or in proportion (pollen—1)	0 36	1 28	1
Number of routine tests in each case	16	148	42
Or in proportion (pollen—1)	0 38	3 52	1
Positive skin tests if number of tests for each group were equal	1267	482	1330

* Including dermal, intradermal, "borderline," late reactions and repeated testing

while in only 17 per cent did the first attacks of asthma occur during other months. If we check these data with the approximate time of pollen peaks in Detroit, we can well appreciate the rôle which pollen plays in the production of chronic asthma (Figure 1). This is corroborated further by the

Differential pollen counts for Detroit 1929



Date of onset of first attack in 65 patients with chronic asthma

FIG 1 Periods of onset of asthma as compared to periods of pollen incidence.

fact that the largest number of asthma sufferers in this locality present themselves for treatment during or shortly after these peaks, namely in July, September and October

The rôle of pollen in the production of asthma is somewhat at variance with that of other substances. It is apparent that other antigens can be eliminated from our surroundings with much less difficulty than pollen. If a spontaneous desensitization to food or other antigens is possible through continuous exposure, this mechanism of recovery is entirely out of the question with pollen because of its periodic appearance and disappearance from the air. Moreover, in pollen allergy there is, during the season, a continuous absorption of antigen throughout day and night which is again in contrast with the mode of absorption with most other allergens—particularly food. All these factors make the case of severe pollen asthma much more refractory to therapy than other types of “extrinsic” asthma.

“POST-POLLEN” ASTHMA

Before further enlarging on this subject it is necessary to draw attention to a definite type of asthma which, although unsatisfactorily explained at present, seems to be very pertinent to the question of pollen sensitization. In my experience with asthma, the most persistent resistance to treatment is encountered during the months of October and November. I have made several attempts to investigate this phenomenon. In 1929 to 1930, I tested 25 patients with various leaf extracts assuming some relationship of the falling and disintegration of the leaves to this type of asthma. While in one case (M G) a definite reaction to a chestnut leaf was obtained, desensitization in the following year proved to be a failure. I further attempted to culture molds and fungi from these leaves, checking the organisms obtained with those found in the sputum of patients. Several distinct skin reactions were observed, in treating one patient (W M) with mold extracts, I encountered a definite constitutional reaction which pointed to an etiological connection. On the whole, however, the data were inconclusive.

I have noted repeatedly that patients with seasonal pollen asthma, without marked additional sensitization, when living in pollen-free rooms may present symptoms for from two to three weeks after the disappearance of pollen from their surroundings. If one considers that during the end of the ragweed season many are subject to development of sensitization to cold and to bacterial or fungi infection, it is rather apparent that infection of the nasal and bronchial mucosa with bacteria and molds may play a large part in the continuation and aggravation of the seizures and in addition may give rise to other secondary sensitizations, such as to epidermals, dusts and foods. In other words, it appears that chronic asthma very often starts with a primary pollen sensitization which then becomes aggravated by infections and continues through the production of secondary sensitizations of other types.

METHOD OF TREATMENT

Of the series of 121 consecutive patients with perennial asthma, 26 were selected who were of the most severe type and had been under continuous care for at least 12 months. Their asthma had been continuous, with an average duration of six and one-half years. Some of these cases were in extremis when first seen. They all had had previous treatment for asthma either by myself or other physicians, particularly by the use of elimination diets, vaccine-therapy, roentgen-ray treatment, nasal operations, and drugs, especially iodides and stramonium. Most of these patients were chronic users of epinephrine, opiates, and ephedrine.

Close questioning revealed the fact that in 10 there was no variation of symptoms throughout the year, while in the 16 there were definite exacerbations of symptoms during the months indicated in figure 2. This chart

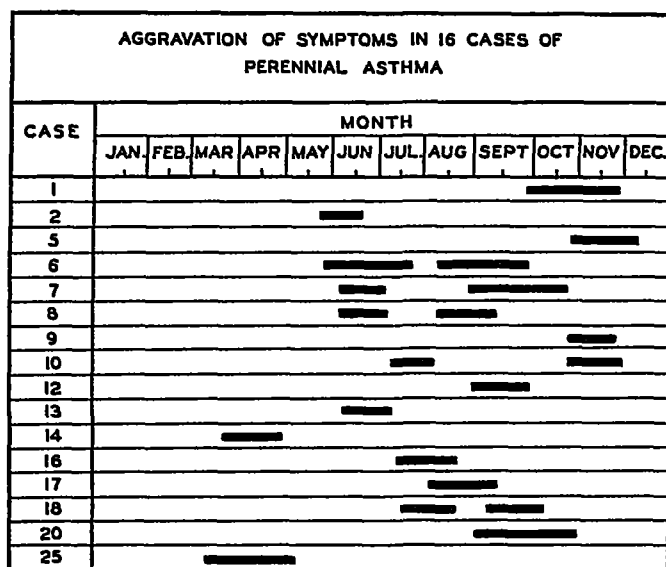


FIG 2

again indicates the relationship of chronic asthma with the pollen content of the air. In 11, scratch tests were negative when the patients first came under my observation. On repetition of the tests, and substitution of the scratch method by intradermal, conjunctival and passive transfer tests, all but two patients were found to react positively to pollen. The pollen injections were given in the same manner as in hay fever patients. Treatment was started at any time of the year, namely as soon as the patients came under my care. The patients received a mixture of short and long ragweed timothy, June grass, and orchard grass, together with such other pollens as were indicated by their history and skin tests. English plantain and some of the tree pollen were frequently used. In those in which skin tests and history gave no clue as to treatment, all the above pollens were included. An attempt was made to reach the maximum dose of the pollens at the beginnings of their respective seasons.

The dose employed is, I believe, a very important factor in successful treatment. When the patient presented himself during the pollen season, very small amounts of pollen extracts were used at frequent intervals, adjusting the dose cautiously by watching for the appearance of local reactions and general response to treatment. In treatment during the season the objective was to obtain a small wheal rather than to reach a large final dose.

In preseasonal treatment the doses were considerably higher than during the hay fever season, ranging on an average between ten to thirty thousand units. Some of the patients received as a maximum dose 3 c c of the 2.5 per cent extract (75,000 units) of each pollen. When the larger doses were given it was sometimes necessary to inject the extract of one pollen on one day and that of the other on the next in order not to produce too much local swelling. In a few cases it was necessary to direct treatment towards factors other than pollen, particularly within the first weeks after the patient presented himself for treatment. However, no other form of therapy was carried on systematically for any length of time. An effort was made to record such additional measures in table 2.

REACTIONS

The impression has been previously recorded⁸ that patients with chronic asthma do not as a rule present the typical anaphylactic reaction following a pollen injection. In this series of cases this was again demonstrated. Patients whose doses were not correctly adjusted developed merely an increase in their asthmatic manifestations, usually within one-half to three hours, instead of the customary reaction of urticaria, sneezing, cough, etc.

Accordingly, care has to be exercised to increase dosage cautiously and to avoid the accident of an intravenous injection. In treatment during the season especial caution should be used. It has been observed on several occasions that treatment with ragweed extracts was greatly hampered during the peaks of the spring pollen season, because of the great susceptibility of the patient to reactions, probably due to absorption of both pollens.

Considering all of these factors, most of which have been outlined before, I merely wish to stress the fact that an aggravation of symptoms by the injections should always be regarded as an indication that the pollen administered will finally be effective, but that its dose should be gauged more cautiously.

RESULTS

During an average time of observation of 23.4 months, of 26 cases treated (table 4) six were entirely free from attacks, nine had one or two minor attacks during the year, seven were improved but are still wheezing occasionally, four had no relief whatsoever. In some cases the results were spectacular. For instance, Case 21 had taken 20 to 30 c c of epinephrine daily before he came under my care, resulting in large abscesses on both arms. Case 20 had been greatly emaciated and despondent. In both in-

TABLE II

No	Age	Sex	Years of Asthma	Name	Began Treatment On **	Results *	Skin Reactions to Pollen		Remarks
							On First Testing	Repeated † Tests	
1	15	M	9	B C	7-2-29	++ Entirely free from asthma	Pos		No more treatment since Oct 1931
2	14	F	12	A M	3-5-31	++ Entirely free since June 1931	Pos		
3	66	F	8	M K	2-12-31	+ One attack in Jan 1932 due to shrimps, otherwise no asthma	Neg	Pos (I)	
4	49	F	9	F G	9-15-31	- No relief	Neg	Pos (I)	House dust injections relieved
5	11	M	4	R E	1-30-31	+ Two attacks Feb and Nov 1931, otherwise free	Pos		
6	55	F	9	H U	3-12-31	+ Free except for one slight attack, tree season, 1932	Neg	Pos (D)	
7	8	M	4	W M	10-3-31	+ Much relieved but slight recurrence July 1932 and Nov 1931	Pos		Had four injections of yeast extract
8	41	M	20	F M	12-1-30	+ Slight wheezing in Dec 1930, otherwise free	Pos		
9	26	M	8	H R	9-18-29	++ Nasal catarrh Nov 1931, otherwise completely free	Neg	Pos (D)	Temporary food elimination
10	50	F	3	W C	6-22-31	+ Considerable relief but still an occasional attack (infectious)	Neg	Neg (DICP)	Received autogenous vaccine recently
11	48	F	9	G L	5-27-31	+ Much improved since Feb 1932 but not free	Pos		

* ++ Excellent
+ Good or fair
- No

** Under observation until January 1933

† (D) Dermal, (I) Intradermal, (C) Conjunctival, (P) Passive transfer

TABLE II (Continued)

No	Age	Sex	Years of Asthma	Name	Began Treatment On **	Results *	Skin Reactions to Pollen		Remarks
							On First Testing	Repeated † Tests	
12	22	M	9	R B	1-8-28	+ Slight attack in July 1932, otherwise free + Slight attacks but much improved	Pos	Neg (DI)	Sensitive to numerous al- lergens. Expired following pneu- monia.
13	36	F	6	R L	9-18-31		Pos		
14	55	M	8	J C	6-13-31	- No relief whatsoever	Neg		
15	43	F	6	L B	9-17-31	+ Much relieved but slight recurrences at height of timothy and ragweed seasons	Neg	Pos (I)	
16	46	M	20	W H	5-21-31	+ Entirely free but recurrence at timothy and ragweed seasons 1932	Neg	Pos (I)	Attacks readily controlled by daily injections
17	11	F	7	J F	1-22-31	+ Three slight attacks in 1932, otherwise completely free	Pos		Recent attacks due to peanuts
18	8	M	5	V P	5-10-30	- No improvement	Pos		
19	15	F	5	M S	2-22-30	++ Completely free	Pos		
20	13	F	7	E G	9-24-30	+ Bronchitis in June, slight wheezing on Sept 4, 1932, otherwise completely free	Pos		
21	42	M	4	R D	5-5-31	+ Well for 15 mos , discontinued treatment, relapse during ragweed season 1932	Neg	Pos (C)	Had taken 30 c c epinephrine daily before under my care
22	47	M	4	A W	12-9-31	+ Some relief but attacks still persistent.	Neg	Pos (D)	Living near chicken coop, strong reaction to chicken feathers
23	12	M	4	M F	1-2-31	- No relief	Neg	Pos (I)	
24	14	F	12	B M	6-4-31	++ Free from asthma	Pos		
25	45	F	3	L S	9-10-31	+ Little response at first, much improved since April 1932	Pos		
26	11	M	4	J V	11-15-31	++ Free from asthma	Pos		

stances, two small injections of pollen extract initiated immediate relief which lasted for more than 14 months. It is interesting to observe that most of those patients who did not recover completely had recurrences at the height of the pollen seasons. This probably indicates that either an insufficient dose had been given or that the wrong selection of pollens had been made. I do not feel that an overdose accounted for the existence of symptoms, because in most instances further increase of the dose controlled the existing symptoms. Some of the failures are unquestionably due to insufficient attention to other sensitizations. For instance, Case 3 had been free from asthma until one day when she fried and ate oysters which produced an immediate attack of asthma. The greatest resistance to treatment was encountered during the "post-pollen season." In some of the patients who started treatment at this time, several weeks elapsed before the beneficial effect could be noted. As table 3 indicates, those patients who gave positive skin tests responded more readily to treatment than those in whom the testing was negative.

TABLE III
Results According to Skin Reactions to Pollen

Number of Cases	Excellent	Good and Fair	No improvement	Total
Pollen-sensitive on first testing (dermal)	6	7	1	14
Positive on check by dermal, intradermal, conjunctival, and passive transfer tests	2	6	2	10
Negative		1	1	2
Total	8	14	4	26

DISCUSSION

In explaining the results obtained, one could well assume a nonspecific effect of the pollen extract. However, the following considerations weigh against this viewpoint. All patients in this series were sensitive to more than one group of antigens. It is well known that the control of one of the main offensive substances such as a certain food or animal emanation may bring about a marvelous recovery, in spite of the fact that some of the remaining allergens are still at work. Vaughan has noticed that in pollen-sensitive individuals perennial treatment appeared to free the patients from attacks due to other sensitizations. In accord with this experience and with the evidence set forth that pollen can be considered as the most common offender in most cases, we can well expect that the control of the pollen factor will be equally as, if not more successful than the control of any other allergens. With this in mind we can explain the improvement during the winter months when no pollen is in the air. Undoubtedly the prevention of nasal infection during the pollen months tends to counteract the development of secondary factors, particularly infection.

The advocacy of this treatment should not induce us to neglect the value of other measures for the relief of this type of case. In fact, some of the patients recorded here were subsequently further relieved by control of other factors. Comparison, however, of the results of perennial pollen treatment with those obtained by vaccine treatment (Rackemann⁹), food elimination (Rowe¹⁰), and other measures seem to me to warrant that attention to pollen sensitivity be given foremost consideration.

CONCLUSIONS

1 Among 121 cases with chronic perennial asthma, it was found that pollen played the most important part as a causative factor. This was evidenced by a distinct aggravation of symptoms during the pollen peaks, by the history of onset of the first attacks during the time of pollination, and by comparison of the results of the skin tests.

2 Attention is directed to the frequent aggravation of asthma shortly after the pollen season ("post-pollen asthma"). A proper explanation for this type of asthma cannot be given at present.

3 Of the 121 cases, 26 were selected because they presented unusually severe asthma and had been under continuous observation for at least 14 months. Injections with a combination of the extracts of the most important hay fever pollens of this area were given. The results obtained compare favorably with those of any other measure devised so far for treatment of this type of case.

4 Among the 26 patients, the initial tests for pollen by the dermal method were negative in 11. In all but two patients positive tests were obtained by repeated testing subsequently. The therapeutic results were decidedly better in those who gave positive tests at the first testing.

5 In administering pollen extract to asthmatics, attention should be directed to the following points: (1) The maximum dose, as a rule, should be higher than for hay fever patients, (2) Aggravation of the symptoms following injections should be regarded as an indication that the treatment finally is likely to prove successful, but that an overdose has been given, (3) During the height of the pollen season, treatment should be given with the proper precautions recently outlined by others for co-seasonal treatment.

BIBLIOGRAPHY

- 1 DUKE, W. W. Allergy, asthma, hay fever, urticaria and allied manifestations of reaction, 1925, C. V. Mosby, St. Louis.
- 2 WALZER, M. Asthma, in COCA, A. F., WALZER, M., and THOMMEN, A. A. Asthma and hay fever in theory and practice, 1931, C. C. Thomas, Springfield.
- 3 VAUGHAN, W. T. Allergy and applied immunology: a handbook for physician and patient, on asthma, hay fever, urticaria, eczema, migraine, and kindred manifestations of allergy, 1931, C. V. Mosby, St. Louis.
- 4 PESHKIN, M. M. Dry pollen ophthalmic test in pollen asthma and hay fever patients negative to cutaneous tests, Jr. Allergy, 1931, iii, 20-29.

- 5 BROWN, A Perennial treatment of seasonal hay fever, *Jr Allergy*, 1931, *iii*, 113-119
- 6 FIGLEY, K D Continuous method of hay fever treatment, *Jr Allergy*, 1930, *ii*, 39-42
- 7 VAUGHAN, W T Perennial pollen desensitization, *Jr Am Med Assoc*, 1931, *xcvii*, 90-91
- 8 WALDBOTT, G L Systemic reactions from pollen injections, their causes and prevention, *Jr Am Med Assoc*, 1931, *xcvi*, 1848-1851
- 9 RACKEMANN, F M Chronic severe asthma, study of group of cases requiring hospital treatment, *Jr Am Med Assoc*, 1932, *xcix*, 202-204
- 10 ROWE, A H Food allergy, its manifestations, diagnosis, and treatment, *Jr Am Med Assoc*, 1928, *xc*, 1623-1631

RENAL GLYCOSURIA *

By A F FOWLER, M D , C M , *Montreal, Canada*

IN 1931, within a few days, two children were admitted to the children's ward of The Montreal General Hospital with glycosuria. One was a girl, the other a boy. Their ages were four and one-half and five years respectively. In each case the urine, in addition to sugar, contained acetone. The girl had renal glycosuria and the boy was suffering from acute diabetes with severe acidosis (precoma). To have assumed that the girl was a diabetic suffering from acidosis because of the glycosuria and acetonuria, and to have given her insulin without certain precautions, would, to say the least, have endangered her life, whereas, in the case of the boy, insulin treatment was imperative. The purpose of this communication, therefore, is to deal with the general management of such cases. This case of renal glycosuria is also reported because of the age of the child and the opportunity afforded to deal with the problem of renal glycosuria.

CASE REPORT

The child, a white female four and one-half years of age, was admitted to the hospital on May 22, 1931 with a history of vomiting, lassitude, loss of weight, loss of appetite and headache.

The family history was irrelevant, there was no history of diabetes or of glycosuria. The child's past history was also irrelevant, she was born at full term, was breast fed for eight months and the only illness was measles at the age of three years.

The present illness, vomiting, etc., appears to have dated back seven weeks prior to admission to the hospital, the prominent features being periodic attacks of nausea and vomiting. During these attacks the child would refuse food and was kept in bed.

The physical findings were negative except for slight fever ($T=99.2$), drowsiness, undernutrition (weight 28 pounds), an injected pharynx and acetone odor to the breath. The laboratory data were as follows:

Urine Acid reaction, S G—1030, sugar plus, acetone plus, no albumin, microscopic findings, negative

<i>Blood</i> Red cells	3,790,000
White	11,150
Sugar	0.101 per cent
Urea-N	24 mg per 100 c c
Cholesterol	0.119 " "
Wassermann	Negative

Additional Data

Tuberculin Test 1/10 c c 1/1000 O T, negative, 1/10 c c 1/100 O T, negative

* Read before the Seventeenth Annual Clinical Session of The American College of Physicians, February 8, 1933

From the Department of Metabolism, The Montreal General Hospital

X-Rays—*Chest*—Negative, except for moderate and generalized increase of bronchial and peri-bronchial thickening

Sella Turcica—Rather small No destruction of floor or of clinoid processes

Fcet—Epiphyses normal

The combination of glycosuria, acetonuria, drowsiness, leukocytosis and increase of blood urea nitrogen suggested diabetes with acidosis. Opposed to diabetes there was the normal blood sugar and opposed to severe acidosis of diabetes was the absence of albuminuria. As is well known, albumin and a shower of casts in the urine is an almost invariable finding in the diabetic approaching coma. The impression, therefore, was that the child was suffering from some gastrointestinal upset, commonly met with in childhood, and that the fever and leukocytosis were the result of the latter or due to the injected pharynx. The child was, therefore, given the usual ward diet for her age—a diet liberal with respect to carbohydrate. The following day, the urine, though it contained sugar, was free of acetone and the blood sugar, obtained in the fasting state, was again normal.

The subsequent clinical history is irrelevant except for the glycosuria. The acetonuria on admission was regarded as a starvation phenomenon, as it disappeared following the institution of a liberal carbohydrate diet without the aid of insulin. Since the glycosuria persisted and appeared to bear no relationship to the clinical picture, renal glycosuria was suspected. The child was, therefore, subjected to the routine examination of such cases in this Clinic, as previously described by Rabinowitch.¹

A diet was prescribed containing definite quantities of carbohydrate, fat and protein. The carbohydrate content was then gradually increased and blood and urine sugar estimations were made daily. The combined data obtained between May 30 and June 9 are recorded in table 1. The following will be noted.

(a) Glycosuria was *constant*. This is shown in the periodic examinations throughout the day. Samples were collected as follows: 8 a.m. to 12 noon, 12 noon to 5 p.m., 5 p.m. to 10 p.m., 10 p.m. to 7 a.m., and 7 a.m. to 8 a.m. The purpose of this method of sampling was to determine separately the effects of breakfast, the noon and evening meals, and the metabolism during the night and that in the fasting state.

It may here be observed that the sugar was identified as glucose.

(b) The amount of sugar excreted was small, ranging between 1.9 and 7.4 grams per 24 hours. A possible source of error must be considered here in that the collection of urine was not quantitative, some was lost. It will, however, be noted that for corresponding volumes of urine the total amounts of sugar were approximately the same regardless of the carbohydrate content of the diet.

(c) There was no relationship between the intake and output of sugar, the urine contained no more sugar when the diet contained 300 grams of carbohydrate than when the intake was 150 grams.

(d) The blood sugars were *always* normal in the fasting state.

(e) Acetone was found in the urine during the first three days of observation only. It disappeared with the disappearance of the vomiting and starvation.

On June 9, as it was considered that the child had acquired a reasonably good store of glycogen, a blood sugar time curve was obtained with the following results.

In the fasting state the blood sugar was normal, namely, 0.100 per cent. Twenty-five grams of glucose were then given by mouth with the following results.

Time			Blood sugar (per cent)
30	minutes	after ingestion	0.125
60	"	"	0.156
120	"	"	0.091
150	"	"	0.100

TABLE I
Effect of Diet on Blood and Urine Sugar

Date	Urine Sugar					Glycosuria * (periodic)					Blood Sugar (per cent)	Diet			Remarks
	Volume	Per cent	Grams	Acetone	Diacetic acid	8 a m to 12 noon	12 noon to 5 p m	5 p m to 10 p m	10 p m to 7 a m	7 a m to 8 a m		Carbohydrate	Fat	Protein	
May 30	115	2.5	2.7			++	++	++	++	++	0.086	150	53	56	25 c c 40% glucose every two hours for 5 doses " " " " " hour for 10 doses " " " " " 15 " Blood sugar time curve
31	170	1.3	2.2	++		++	++	++	++	++	0.101	200	53	56	
June 1	195	2.7	5.3	++		++	++	++	++	++	0.122	250	53	56	
2	155	3.8	5.9	0		++	++	++	++	++	0.111	300	53	56	
3	75	6.2	4.6	0		++	++	++	++	++	0.105	300	53	56	
4	130	5.0	6.5	0		++	++	++	++	++	0.120	300	53	56	
5	180	4.1	7.4	0		++	++	++	++	++	0.101	300	53	56	
6	230	1.3	3.0	0		++	++	++	++	++	0.113	300	53	56	
7	75	2.5	1.9	0		++	++	++	++	++	0.084	300	53	56	
8	150	3.5	5.2	0		++	++	++	++	++	0.116	300	53	56	
9	105	4.1	4.3	0		++	++	++	++	++	0.100	300	53	56	

* Minus signs indicate no specimen obtained

The urine was collected at the above periods and sugar was found in all specimens

In view of the above findings a full hospital diet was prescribed and the child was kept under observation until July 13. During this time the urine *always* contained sugar and the amount never exceeded 10 grams per 24 hours. There was no acetone or diacetic acid. The blood sugars were always normal in the fasting state.

On July 10, one month after the previous blood sugar time curve, another curve was obtained with the following results:

In the fasting state the blood sugar was normal, namely, 0.088 per cent. Twenty-five grams of glucose were then given by mouth with the following results:

Time				Blood sugar (per cent)
30	minutes	after	ingestion	0.113
60	"	"	"	0.133
120	"	"	"	0.106
150	"	"	"	0.087

The urine was collected at the above periods and sugar was again found in every specimen.

Because the child failed to cooperate, data with respect to the respiratory metabolism were not obtained. In view, however, of the clinical course and the laboratory data a tentative diagnosis of renal glycosuria was made and the child was discharged from the hospital on July 14. The mother was instructed to bring her to the Clinic for Diabetes for observation periodically.

The child was not seen or heard of again until March 1932—eight months later. The reason given by the mother for her failure to follow instructions was that the child was well. During the interval, there were no restrictions whatever with respect to her diet. She was again admitted to the hospital for observation.

On admission, it is of interest to note that the urine, in addition to sugar, again contained acetone. This was a starvation phenomenon, the child, on learning that she was to be admitted, had refused most of her food for three days.

The observations made were practically identical with those of the former admission and with practically identical results. The combined data are shown in table 2. It will be noted firstly, that following ingestion of liberal quantities of carbohydrate the acetone again disappeared shortly after admission, secondly, that there was constant glycosuria, thirdly, that there was no relationship between the intake and output of sugar, and lastly that all blood sugars, in the fasting state, were again normal. A blood sugar time curve was obtained on April 2, 1932 with the following results:

In the fasting state the blood sugar was normal, namely, 0.089 per cent. Twenty-five grams of glucose were then given by mouth.

Time				Blood sugar (per cent)
30	minutes	after	ingestion	0.133
60	"	"	"	0.119
120	"	"	"	0.100
150	"	"	"	0.082

The child was discharged on April 2, 1932 and was not heard of until January 17, 1933 when she was brought to the Clinic by her mother. A specimen of urine then showed sugar but no acetone. She was again recommended for admission. On learning that she was to be admitted the child again refused food and on admission the following day, the urine, in addition to sugar, again contained acetone. The data obtained during this admission were essentially similar to those of the two previous admissions. The combined results are shown in table 3. This time, however,

TABLE II
Effect of Diet on Blood and Urine Sugar

Date	Urine Sugar				Glycosuria * (periodic)					Blood Sugar (per cent)	Diet			Remarks	
	Volume	Per cent	Grams	Acetone	Diacetic acid	8 a m to 12 noon	12 noon to 5 p m	5 p m to 10 p m	10 p m to 7 a m		7 a m to 8 a m	Carbohydrate	Fat		Protein
March 23	315	1.2	3.7		0	++	++	++	+	tr	0.052	150	50	56	25 c c 40% glucose every two hours for 5 doses " " " " " hour for 10 doses " " " " " 15 " " " " " " " Blood sugar time curve
25	590	0.5	2.9	++	0	++	++	++	++	tr	0.079	150	50	56	
26	250	0.9	2.2	++	0	++	++	++	++	tr	0.095	150	50	56	
27	190	0.9	1.7	++	0	++	++	++	++	tr	0.111	150	50	56	
28	282	2.1	5.9	++	0	++	++	++	++	tr	0.108	150	50	56	
29	200	3.3	6.6	++	0	++	++	++	++	tr	0.108	200	50	56	
30	130	4.4	5.7	0	0	++	++	++	++	tr	0.095	250	50	56	
31	150	3.3	4.9	0	0	++	++	++	++	tr	0.095	300	50	56	
1	150	3.8	5.7	0	0	++	++	++	++	tr	0.091	300	50	56	
2	239	2.3	5.5	0	0	++	++	++	++	tr	0.089	300	50	56	

* Minus signs indicate no specimen obtained

TABLE III
Effect of Diet on Blood and Urine Sugar

Date	Urine Sugar					Glycosuria (periodic)					Blood Sugar (per cent)	Diet			Remarks
	Volume	Per cent	Grams	Acetone	Diacetic acid	8 a m to 12 noon	12 noon to 5 p m	5 p m to 10 p m	10 p m to 7 a m	7 a m to 8 a m		Carbohydrate	Fat	Protein	
Jan 19	460	21	97	0	0	+++++	+++++	+++++	+++++	+++++	0.111	150	50	56	25 c c 40% glucose every two hours for 5 doses
20	812	21	170	++	0	+++++	+++++	+++++	+++++	+++++	0.069	200	50	56	" " " " hour for 10 doses
21	545	31	169	++	0	+++++	+++++	+++++	+++++	+++++	0.111	250	50	56	" " " " " 15 "
22	689	50	344	tr	0	+++++	+++++	+++++	+++++	+++++	0.113	300	50	56	" " " " " "
23	472	50	236	0	0	+++++	+++++	+++++	+++++	+++++	0.097	300	50	56	" " " " " "
24	450	33	148	0	0	+++++	+++++	+++++	+++++	+++++	0.091				Blood sugar time curve

throughout the period of observation the child had fever of unknown origin, the temperature ranging between 99° and 100° F. The child refused most of her food during the first few days and on one occasion the urine showed sugar, acetone and diacetic acid. Following liberal diet with glucose feedings the acetone disappeared. Again, glycosuria was constant and the amounts of sugar excreted daily were small. All blood sugars were again normal in the fasting state and on January 24, 1933 a blood sugar time curve was obtained with the following results:

In the fasting state the blood sugar was normal, namely, 0.093 per cent. Twenty-five grams of glucose were then given by mouth.

Time	Blood sugar (per cent)
30 minutes after ingestion	0.143
60 " " "	0.158
120 " " "	0.109
150 " " "	0.109

SUMMARY OF CASE

To summarize, we have here a child who, when first seen, was four and one-half years of age and is now six years old, and who has had constant glycosuria as shown by 198 analyses. The sugar has been identified as glucose. The amounts excreted have been always small and not related to the carbohydrate content of the diet. The blood sugars, in the fasting state, have always been normal. In all there have been 33 analyses. Four blood sugar time curves obtained at long intervals of time have been normal. There have been no clinical signs or symptoms to suggest diabetes other than at the first admission to the hospital. At that time, these were readily explained by a gastrointestinal disturbance and injection of the pharynx.

That the acetonuria on each admission was due to the starvation and not to diabetes is suggested from the fact that it disappeared following the administration of food *without* insulin. The best indication, however, of the absence of diabetes is the fact that the child has been on an unrestricted diet for over one and one-half years and is well. As is well known, in juvenile diabetes when in addition to glycosuria the diabetes has reached the stage of ketosis and acidosis, death is the rule within a very short time, unless insulin is administered.

DISCUSSION

As has been repeatedly emphasized in this Clinic and will again be shown, *renal glycosuria is rare*. Cases in which, in addition to sugar, acetone is found in the urine are still more rare, and, as demonstrated in the case just reported, they present difficulties in diagnosis. In renal glycosuria, *acetonuria* is merely a starvation phenomenon and is usually due to persistence in the attempt to free the urine of sugar by restriction of diet or, as in our case, to vomiting and its resultant starvation. Children, as is well known, are particularly susceptible to ketosis. This case, therefore, emphasizes the fact that absence of ketosis is not a necessary criterion for the diagnosis of renal glycosuria. This is contrary to the view still expressed as late as 1931 by Peters and Van Slyke.² Much more important diagnostically than the absence of ketosis is the finding of *constant* glycosuria for, as will presently be shown, with this criterion many cases of so-called renal glycosuria recorded in the literature are excluded.

INCIDENCE

In approximately 4000 cases of glycosuria investigated in the Clinic for Diabetes of this hospital 13 individuals only were ever regarded as renal glycosurics. Six of these cases are, however, now excluded because the conditions do not conform to all of the necessary requirements for such diagnosis. We are, therefore, left with seven cases only—an incidence of 1.75 per 1000 glycosurics. In the fourth edition of "The Treatment of Diabetes Mellitus" Joslin reported 47 cases of renal glycosuria in the first 6000 cases of glycosuria. In the next 3000 cases 19 more were so classified, making 66 in all. As a result, however, of a recent re-investigation of these cases by Marble,⁸ one of Joslin's assistants, and the use of diagnostic criteria similar to those of our Clinic, the number of cases of typical renal glycosuria was reduced to 15. This gives an incidence of 1.66 per 1000, which, it will be observed, agrees very closely with our own. Combining the data of the two clinics, it will be observed that 22 cases only have been found among approximately 13,000 glycosurics. That many cases diagnosed as renal glycosuria eventually prove to be otherwise is shown by experience in this clinic. Six such individuals previously diagnosed as renal glycosuria elsewhere were subsequently admitted to this hospital with the signs of active diabetes. In two of these cases, at the time of admission, the patients were in precoma. In another case the individual had developed a cataract.

The youngest renal glycosuric recorded in the literature is that reported by Paullin and Bowcock.⁴ Glycosuria was discovered when the child was two years old and it has been constant since. Goldbloom⁵ reported a child 20 months old and Williams⁶ a child three and one-half years of age. These last two cases are, however, excluded, according to our criteria, as in both it is stated that the urine subsequently became free of sugar.

DIAGNOSTIC CRITERIA

The diagnosis of renal glycosuria involves the use of laboratory procedures which as a rule are available only in hospitals. The safest rule for the physician in general practice is, therefore, to assume that every glycosuric is a diabetic until proved otherwise, as we have repeatedly emphasized, it is much safer to underfeed a normal individual than to overfeed a diabetic.

The criteria for the diagnosis of renal glycosuria are as follows

- 1 Glycosuria must be *constant*
- 2 The type of sugar found in the urine must be identified as glucose
- 3 There must be little or no relationship between the intake and excretion of sugar
- 4 There must be no clinical signs or symptoms of diabetes
- 5 There should, ideally, be no family history of diabetes

- 6 The blood sugar in the fasting state must always be normal
- 7 The blood sugar time curve after the ingestion of glucose must be within normal limits
- 8 The rate of utilization of sugar, as determined by the respiratory metabolism, must be normal
- 9 The individual must not subsequently develop diabetes

These conditions will now be considered in greater detail

1 Glycosuria must be constant It seems desirable, if renal glycosuria is to be regarded as a clinical entity, that this criterion should be insisted upon Joslin agrees with this view, and in the 15 cases reported from his clinic and in the seven from this clinic, glycosuria was found constantly

2 The type of sugar found in the urine must be identified as glucose This requires no comment

3 There must be little or no relationship between the intake and excretion of sugar As the collection of urine in the child reported here was not strictly quantitative, the data of another case, an adult, are shown in table 4 to demonstrate this phenomenon

TABLE IV
(Female, Age 22)

Date	Vol	Urine		Blood	Diet			Remarks
		Sugar %	Sugar gm	Sugar %	C	F	P	
March 25	250	3.1	8	0.085	150	140	60	(Specimen of urine incomplete)
" 26	900	2.5	22	0.111	250	140	60	25 c c 40% glucose q 1 h X 10 doses
" 27	1050	3.3	35		350	140	60	50 " " " " " "
" 28	1300	3.8	49	0.113	450	140	60	75 " " " " " "
" 29	1050	3.5	37	0.109	450	140	60	" " " " " " "
" 30	775	3.8	29	0.092	450	140	60	" " " " " " "
" 31	650	3.3	21	0.095	450	140	60	" " " " " " "
April 1	650	4.1	27	0.120	450	140	60	" " " " " " "
" 2	1300	3.3	43	0.095	450	140	60	" " " " " " "

It will be observed that though the carbohydrate content of the diet was increased 100 grams daily, the increase of sugar in the urine was relatively inappreciable On a constant diet of 450 grams carbohydrate, 140 grams fat and 60 grams protein the sugar excretion in the urine varied from 49 to 21 grams in the 24 hours

4 There must be no clinical signs or symptoms of diabetes Signs of active diabetes help to exclude renal glycosuria, but *absence* of such signs are *alone* of very limited value, for they may also be absent in mild diabetes There is an appreciable number of diabetics who present no clinical signs or symptoms other than the glycosuria, though the diabetes may be of long duration In the clinic of this hospital, for example, there have been 71

individuals who had had the disease for 15 years or over. Of them 27 only required insulin. Of the remaining 44 individuals who did not require insulin, 16 had had the disease for 20 years or more. There were seven deaths in this group and in two instances at the time of death the individual required no insulin, the urines were free of sugar and there were no signs of active diabetes, death was due to other causes, such as cardio-vascular disease, etc.

As shown in the child reported here, the problem is not always simple. On admission to the hospital, the child had symptoms suggestive of diabetes, drowsiness, vomiting, leukocytosis, etc. Since renal glycosuria is rare, the safest rule, in general practice, when in doubt, is to administer sugar and insulin. Following such treatment the acetonuria usually disappears rapidly regardless of its cause, and insulin reactions are avoided because of the hyperglycemia induced by the administration of carbohydrates. After the drowsiness and acetone odor of the breath have disappeared and the urine is free of acetone, insulin may be discontinued and the effects of diet alone noted. If acetone reappears insulin and carbohydrate should again be administered simultaneously. When the acetone disappears permanently and diet is found to have no effect on the glycosuria and when the clinical condition is otherwise negative, renal glycosuria may then be suspected but should not be diagnosed in practice with limited laboratory facilities.

5 There should, ideally, be no family history of diabetes. This requires no comment.

6 The blood sugar in the fasting state must always be normal. There are cases in the literature in which the diagnosis of renal glycosuria was made largely because the blood sugar, when obtained in the fasting state, was normal. It might here, therefore, be observed that such blood sugars may be, and are commonly, found in early and mild diabetes, when the glycosuria is either transient or occurs after meals only (post-prandial glycosuria).

7 The blood sugar time curve after the ingestion of glucose should be within normal limits. There is general agreement as to the characteristics of a perfectly normal blood sugar time curve. The vagaries, however, are many and the following case is cited as an example.

A female, aged 22, was admitted to the hospital on March 18, 1932 with complaints referable to the gall-bladder and a tentative diagnosis of chronic cholecystitis was made. She was known to have had glycosuria prior to admission. There were no other signs or symptoms to suggest diabetes. A blood sugar time curve was obtained with the following results:

In the fasting state the blood sugar was normal, namely, 0.083 per cent and the urine contained sugar. One hundred grams of glucose were then given by mouth.

Time				Blood sugar (per cent)	Urine sugar
30 minutes	after	ingestion		0.117	plus
60	"	"	"	0.192	"
120	"	"	"	0.200	"
150	"	"	"	0.166	"

The curve was abnormal, there was an abnormally high peak and at the end of two hours the blood sugar was still increased. On the day of the test, however, the patient had an upper respiratory infection with slight fever. This curve could also have been due to pancreatic disturbance secondary to the cholecystitis. The carbohydrate metabolism was then investigated as outlined above and is shown in table 4. It will be observed that no relationship was found between the intake and output of sugar. The diet of 450 grams carbohydrate, 140 grams fat and 60 grams protein was continued for 18 days, after which a second blood sugar time curve was obtained. During the interval the patient had slight febrile reactions on a number of days and also on the day of the test.

In the fasting state the blood sugar was normal, namely, 0.111 per cent and the urine contained sugar. One hundred grams of glucose were then given by mouth with the following results:

Time				Blood sugar (per cent)	Urine sugar
30	minutes	after	ingestion	0.153	plus
60	"	"	"	0.166	"
120	"	"	"	0.153	"
150	"	"	"	0.149	"

It will be observed that again there was evidence of disturbed carbohydrate metabolism. A cholecystectomy was subsequently performed and our Pathologist, Dr. L. J. Rhea, reported "chronic cholecystitis." For the following 10 months the patient was on an unrestricted diet. A third blood sugar time curve was then obtained with the following results:

In the fasting state the blood sugar was normal, namely, 0.091 per cent and the urine contained sugar. One hundred grams of glucose were then given by mouth

Time				Blood sugar (per cent)	Urine sugar
30	minutes	after	ingestion	0.112	plus
60	"	"	"	0.125	"
120	"	"	"	0.131	"
150	"	"	"	0.111	"

It will be observed that the response to glucose ingestion was now perfectly normal. In this case the following additional points are of interest: (a) Every specimen of urine examined contained sugar—48 analyses in all, (b) the blood sugar in the fasting state was always normal—28 analyses in all, (c) the respiratory metabolism was normal, and (d) the disturbance noted in the blood sugar time curve disappeared with removal of the infected gall-bladder. The observations of Williams and Dick⁷ are of interest here. These authors have recently demonstrated experimentally that decrease of carbohydrate tolerance may result from an acute infection, and that such loss of tolerance may be of some duration—several weeks or months. This finding agrees with the experience of this clinic.⁸

8 The rate of utilization of sugar, as determined by the respiratory metabolism, must be normal. Among the criteria for the diagnosis of renal glycosuria which are to be found in the literature the inclusion of this phenomenon is the exception rather than the rule. Finley and Rabinowitch⁹ were the first to demonstrate this characteristic of renal glycosuria. Ladd and Richardson¹⁰ subsequently confirmed these findings. Marble³ agrees with Rabinowitch about the importance of this test but points out a possible fallacy in the interpretation of the data, mild diabetics may at times show

no impairment The important fact, however, is that, while the diabetic *may* at times show a normal utilization of carbohydrate the renal glycosuric *must* show it

9 The individual should not subsequently develop diabetes A period of three years of observation from the time of the discovery of the glycosuria has been chosen arbitrarily by some workers as meeting the requirements of this diagnostic criterion⁴ The case reported here has, therefore, as yet to meet one of the requirements

SUMMARY

A case of renal glycosuria with ketosis in a child four and one-half years of age is reported Difficulties in diagnosis and questions of treatment are considered The importance of certain diagnostic criteria is discussed

BIBLIOGRAPHY

- 1 RABINOWITCH, I M Diagnosis of renal glycosuria, *Canad Med Assoc Jr*, 1930, xxii, 329-333
- 2 PETERS, J P, and VAN SLYKE, D D Quantitative clinical chemistry Volume I Interpretations, 1931, Williams and Wilkins, Baltimore, p 193
- 3 MARBLE, A Renal glycosuria, *Am Jr Med Sci*, 1932, clxxxiii, 811-827
- 4 PAULLIN, J E, and BOWCOCK, H M Glycosuria, *Med Clin N Am*, 1929, xii, 1391-1401
- 5 GOLDBLOOM, A Renal glycosuria in an infant twenty months of age, *Canad Med Assoc Jr*, 1924, xiv, 950-952
- 6 WILLIAMS, C T Renal glycosuria, *New Orleans Med and Surg Jr*, 1927, lxxx, 332-333
- 7 WILLIAMS, J L, and DICK, G F Decreased dextrose tolerance in acute infectious diseases, *Arch Int Med*, 1932, l, 801-818
- 8 RABINOWITCH, I M *Ann Surg* (In press)
- 9 FINLEY, F G, and RABINOWITCH, I M Renal glycosuria, a clinical and metabolic study, *Quart Jr Med*, 1923-1924, xvi, 260-273
- 10 LADD, W S, and RICHARDSON, H B Clinical calorimetry XXXVIII The utilization of carbohydrate in a case of renal glycosuria, *Jr Biol Chem*, 1925, lxi, 681-685

EDITORIALS

PAROXYSMAL HYPERTENSION

THERE has existed for many years in the medical literature of foreign countries, and particularly in that of France, evidence of a keen interest among clinicians concerning those abrupt elevations of the systemic blood pressure to which the term paroxysmal hypertension has been applied. Elevations of the systolic blood pressure, often of over 100 mm of mercury in the course of a relatively few minutes, are apt when they occur to produce striking subjective symptoms and to be accompanied by definite dangers. The etiology of such attacks, the mechanism by which they are produced, and the consequences that may ensue are all subjects which are worthy of the internist's attention.

Knowledge of the etiology of this syndrome, paroxysmal hypertension, is still at a stage when only certain clinical associations can be mentioned, without too definite claims as to cause and effect. In the first place, such abrupt rises in blood pressure have been not infrequently observed in a group of cases having in common the factor of a preexisting unstable hypertensive state, i e, in cases of acute glomerulo-nephritis, of eclampsia, of the malignant form of essential hypertension and in an occasional case of chronic lead poisoning. The abrupt rise in pressure in these instances often is accompanied by striking cerebral symptoms, such as violent headache, aphasia, amaurosis, and localized or general convulsive seizures. However, such phenomena probably more often appear at the end of a period of gradually rising pressure rather than in association with a sudden or paroxysmal rise.

It is of interest in this problem of the relationship of the cerebral symptoms to the blood pressure rise that in certain cases of focal cerebral lesions, tumor, internal hydrocephalus and old apoplectic softening, the occurrence has been noted of attacks beginning with a paroxysmal rise in pressure and eventuating in disturbances of consciousness or convulsive seizures. In this same general category should be placed the observations on the abrupt, but scarcely paroxysmal, rise in blood pressure which often accompanies a rapid increase of intracranial pressure due to concussion or to subdural or intraventricular hemorrhage. It has been observed also that occasionally lumbar puncture in disease of the central nervous system leads abruptly to a large temporary rise in blood pressure and the same phenomenon has been reported as an anomalous occurrence in connection with the administration of spinal anesthesia.

The mechanisms that underlie these associations of paroxysmal hypertension with disturbances in the central nervous system are still a matter of conjecture, but it would seem that the relationship is a highly significant one.

Attacks of paroxysmal hypertension occur even more frequently in a quite different clinical association, i e , with disease of the coronary arteries and the aortic valves. The clinical physiognomy of the attacks in these instances is dominated by the effect upon the heart, of cerebral symptoms only throbbing headache is apt to be noted. The rise in blood pressure in these cases entails a sudden overload upon the left ventricle of a damaged heart. The myocardium may still be competent enough to meet the demand through the high pressure period, and if this is so only precordial distress and cardiac overaction are subjectively noted by the patient. The beginnings of acute incompetence of the left ventricle are accompanied, however, by some degree of anginal pain and by urgent dyspnea due to pulmonary congestion. If more complete failure of the ventricle follows, then pain subsides, dyspnea becomes intense and acute pulmonary edema may appear. At the same time the high blood pressure, which is itself dependent upon the effort of the left ventricle, falls slowly or abruptly. In the more seriously damaged hearts failure occurs before any great height of blood pressure is attained, initial pain may be lacking, dyspnea may be urgent from the start and pulmonary edema exhibit itself almost at once. A paroxysmal elevation of blood pressure, slight or great, depending upon the degree of cardiac competence, is the first event in the majority of those attacks which go labelled as angina with dyspnea, cardiac asthma, paroxysmal dyspnea, and acute pulmonary edema. In such cases in which the rise in pressure has been observed, when autopsy has been performed it has disclosed quite uniformly an advanced coronary sclerosis, very commonly with evidence of old cardiac infarction. Occasionally syphilitic coronary occlusion may be present. Entirely similar attacks have been reported in rheumatic aortic insufficiency but without postmortem data on the state of the coronaries. The cause of the attacks of paroxysmal hypertension in all these cases is still purely a matter for speculation.

There occur also moderately severe attacks of paroxysmal hypertension in patients, usually in the younger age periods, in whom no evidence of organic disease is present. Precordial distress, slight dyspnea and headache may accompany the rise in pressure but more serious sequelae are not observed. Disappearance of the attacks after a period of time seems usually to occur. A basis in the emotional life of the patient has been suggested but tangible evidence of such a disturbance is not always obtainable.

There is finally one type of paroxysmal hypertension in which the cause of the attacks is quite well known. A small number of cases have been reported in which sudden and violent rises in blood pressure have occurred as the result of the presence of a tumor of the medulla of the adrenal. In several of these cases the tumor has been removed operatively and the patient freed permanently of the attacks. These tumors are composed of chromaffine cells and have been shown to contain adrenalin in large amounts. The intermittent discharge of this adrenalin content would satisfactorily explain the paroxysmal rises in blood pressure. The effects of the excessive

risks in blood pressure in these otherwise normal patients are of interest. Violent headaches may accompany the attacks, and acute pulmonary edema has in several instances been the cause of death.

THE MORTALITY RATE IN UKRANIA

THE GENERAL interest as to the progress of the great social experiment in Russia and the difficulty of obtaining any exact measure of its degree of success or failure make it seem worth while to draw attention to some rather striking figures recently published,¹ which deal with the evolution of the mortality rate in Ukraina.

The author of this analysis of the Ukrainian mortality rate, M. Ptoukha, a member of the Academy of Science of that country, states that prior to the middle of the decennium 1890–1900 no significant fall in the mortality rate can be detected. From 1895 until 1914 the mortality rate showed a relatively steady decrease and in the period 1911–1914 it was only 71.6 per cent of its height during the period 1891–1895. An analysis of this period of improvement indicates, however, that a coincident decrease in the birth rate in part is accountable for the figures. In the age period 0–14 a definite lowering of the death rate was detectable, but in the adult age groups little change was observable, and the mortality rate among those over 54 years was actually increasing.

During the World War and the period of ensuing civil war lasting until 1921, the figures available indicate that such improvement in the mortality rate as had occurred between 1895 and 1914 was lost, so that at the beginning of the period of reconstruction the mortality rate was again at least as high as in 1896–1897, the years of a complete census. The author therefore feels that in utilizing the census of 1896–1897 for comparison with that taken in 1926–1927 he is in effect comparing the mortality rates of Ukraina before the Soviet regime and after it had exerted its influence for five years. There is a certain ingenuousness to this hypothesis, the results, however, are none the less interesting.

In comparing the two above periods, the author finds that for the stationary population there was a fall of mortality rate of 21 per cent for males and 24.5 per cent for females. The improvement was most marked in the cities where the rate fell 36.6 per cent for males and 36.1 per cent for females. The life expectancy in the country at large for a new-born male was increased by 10 years and for a new-born female by 12 years.

The reduction in infant mortality (0–1 year) was marked. The mortality rate for male infants in the country at large fell 33.2 per cent and for female infants 34.1 per cent. This improvement was greatest in the industrial centers rather than in the country. For male infants in the four large cities the fall in death rate was 57 per cent and for female infants 58.2 per cent.

¹ ПТОУХА, М. Evolution de la mortalité en Ukraine avant l'époque du premier plan quinquennal, Jr. du Cycle Méd., Kyiv, 1932, II, 754–757.

Among children of 1-9 years prior to the Soviet regime the mortality rate due to epidemic intestinal disease was always high. A comparison of the two periods chosen shows that there has occurred a fall in the mortality rate of 40 per cent in this age group. In the adult age group, 20-59 years, the interesting observation was made that whereas the mortality rate for men fell 18.8 per cent, that for women fell 38.4 per cent. In earlier periods in Ukraina the death rate for women in this age group had been 8.15 per cent higher than that for men, whereas in 1926-1927 it was found to be 19 per cent lower than the male mortality rate.

The author states that these improvements in the mortality rates are greater than those that have occurred in analogous periods in France, Italy, England, Japan or the United States. He attributes the improvement to the active interest of the Soviet regime in public health measures, particularly in control measures against epidemics, and in the establishment of institutions for the protection of maternity cases and for the care of infants and children.

The record as stated seems to afford Ukraina just cause for pride. From such uncertain reports as have come from that large walled-off section of our world, there has been reason to doubt whether the social experiment in progress there was conducive to either the health or happiness of the citizens. Here, at least, is some tangible evidence that in the first respect definite advances are being made.

In the last paragraph of the author's article he quotes Stalin who, in addressing the Central Committee of the Sixteenth Assembly of the Communist Party, attributed the achievement of the lowered mortality rate to the repartition of the national revenue which had given to the laboring classes the opportunity of improving the sanitary and hygienic conditions of their lives. In 1929-1930, stated Stalin, 98 per cent of the national income went to the industrial workers and peasants and only 2 per cent to the class of exploiters. Those who believe that only a government which acts in a spirit of justice to all and favor to none is likely to bring about the happiness of its people may, after the above statement, still retain some doubts as to the ultimate success in this respect of the Soviet Republics. We should like at least to know how large a percentage of the population was included in the class which received only 2 per cent of the national income and what the mortality rate was in this class in the period under discussion.

REVIEWS

Nervous Breakdown By W. BERAN WOLFE, M.D., Director of the Community Church Mental Hygiene Clinic, New York City 240 pages Farrar and Rinehart, New York Price, \$2.50

This very attractively written "handbook" will undoubtedly receive both commendation and criticism and it will be widely read because it treats of a subject ever present in society. Unfortunately, the author's discussion of human behavior would lead a lay reader to the belief that the straightening out of a "nervous breakdown" is a very simple matter. Although the author attempts to disarm criticism by making some sweeping statements about quackery, he himself seems to place psychiatry on a pedestal and to imply that psychiatrists have an open sesame. He says in his preface "If you cannot find any evidence of physical or organic disease, consult a psychiatrist." The author also says on page 184 "I wish we could talk it over face to face." And on the next page "If you like, you can sit down and write me your life story and thus hold a community conversation with me. You can always do that if you are lonely." Since the neurotic individual is continually looking for a sympathetic ear there will no doubt be a bountiful response to his advice.

The author has presented in this volume some very graphic cases and expresses on the whole a very sound viewpoint. Very few psychiatrists will take an exception to his explanations of mechanisms as he does not align himself with any specific school of psychology. His discussions in the last two chapters are the weakest part of his book, but the first five chapters will keep the readers interested without difficulty. This handbook will at least stimulate the reader, whether professional or lay, to a more extensive reading of the subject of why people behave the way they do.

J. L. McC

Urine and Urinalysis By LOUIS GERSHENFELD, Ph.D., B.Sc., P.D., Professor of Bacteriology and Hygiene and Director of the Bacteriological and Clinical Chemistry Laboratories at the Philadelphia College of Pharmacy and Science 272 pages, illustrated with 36 engravings Lea and Febiger, Philadelphia 1933 Price, \$2.75

This book has been written, according to the author, to meet the needs and the requisites of graduates in pharmacology, chemistry, bacteriology, the nursing profession, technicians, and many practitioners in medicine "interested solely in the performance of urinalyses" and hence anxious to have an up-to-date monograph on this subject.

Following a brief historical consideration of urinalysis and a very cursory description of the internal structure and function of the kidneys, various chapters are devoted to the physical and chemical composition of the urine, qualitative tests of various sorts, quantitative estimations, the microscopic examination of urine, and special tests under which are included the analysis of urinary calculi, tests for inorganic metallic poisons, bacteriologic investigations, and tests of various sorts for renal function.

The content of the book is well though tersely presented. The tests advised are, for the most part, the standard ones which have been in existence for many years, both qualitative and quantitative in character. No gross inaccuracies were discovered. Not much space is devoted to the interpretation of the various tests, and the many possible sources of error, though one would scarcely expect the inclusion of such matter, in view of the fact that apparently the book has been written for the technician who performs the tests, but who is not required to interpret the clinical value.

of the results. The book can be recommended as fulfilling precisely those purposes for which it was written.

S R M

A New Approach to Dietetic Therapy By EUGENE FOLDES, M D, Formerly Assistant Professor of Medicine, University of Budapest, Hungary. xii + 434 pages. Richard G. Badger, Boston, 1933. Price, \$5.00.

The author believes that a disordered water and mineral metabolism is responsible, in whole or in part, for many disease conditions. The first part of the book is given over to a discussion of the physiology and general pathology of water and mineral metabolism, the work of the author himself being particularly stressed. His dietetic therapy is directed particularly to the elimination of retained mineral substances. The book contains various novel suggestions. The bibliography is extensive and refers very largely to the German literature. In the opinion of the reviewer the book is a medley of half-baked theorizing, based upon very dubious physiological grounds. Whether the therapeutic claims which the author makes may be justified upon empirical grounds, is, of course, another matter, but to this reader they are not convincing.

G A H

Dietetics for the Clinician By MILTON ARLANDEN BRIDGES, B S, M D, F A C P, in collaboration with RUTH LOTHROP GALLUP, dietitian, foreword by HERMAN O. MOSENTHAL, A B, M D, Director of Medicine at the New York Post-Graduate Medical School, Columbia University. 666 pages. Lea and Febiger, Philadelphia. 1933. Price, \$6.50.

In spite of the many books on dietetics which are already available, the reviewer feels that Dr. Bridges has justified himself in adding another volume to this literature. In the first place, the book is written with a freshness and candor which are very attractive. The author shows that he is aware not only of the importance of his subject but also of the deficiencies in our knowledge concerning it. The value of diet when definitely known is stressed but no attempt is made to raise dietetic therapy to the level of a panacea. Many data not usually found in similar textbooks are included in this volume and in readily accessible form. The classified tables cover practically all of the chemical constituents.

The dietetic treatment of the separate diseases is presented by a group of contributors. This section of the book is a valuable one. There is of necessity some repetition since each section is self-contained.

In what is said of the treatment of duodenal ulcer it seems that there is over emphasis on meticulous dietary measures. Ambulatory treatment is mentioned, but for the patient to live up to the exacting regulations prescribed it would almost always be necessary that he be hospitalized. For the important disease, ulcerative colitis, no treatment is mentioned, though considerable space is devoted to proctitis, pruritis ani, and spastic colitis.

L M

Diseases of the Mouth By STERLING V. MEAD, D D S, M S, B S, Professor of Oral Surgery and Diseases of the Mouth, and Director of Research, Georgetown University Dental School, Professor of Diseases of the Mouth, Georgetown University Medical School. 932 pages, 18 x 25 cm. C. V. Mosby Co., St. Louis. 1932. Price, \$10.00.

The author has attempted in this volume to meet the needs of students of both medicine and dentistry for knowledge of the various disease processes affecting the

structures of the mouth. Roughly the first third of the book is given up to a consideration of conditions affecting the teeth and the remaining two-thirds to diseases of the soft tissues, lips, tongue, throat, salivary glands, and of the bones, articulations and the maxillary sinuses. The subjects of stomatitis and of tumors of the mouth region are taken up in separate chapters.

The medical aspects of these diseases are discussed in an elementary way which will not be of value to the average medical reader. Space devoted to such topics as the methods of taking the temperature, counting the blood cells, and using the routine bacteriologic smears is waste space as far as he is concerned. On the other hand the average medical student will profit by the discussion of diseases and abnormalities of the teeth.

To the reviewer, the chapters on the diseases of the lips, tongue, throat, etc. are disappointing. The descriptions of the appearance and characteristics of the various lesions are too vague to be of assistance. The clinical course of these lesions is dealt with only in the briefest and most inadequate manner. The illustrations to these sections are, however, often excellent. The relation of the section on diseases of the blood to the subject of the book is not made as apparent as it should be. For example, in discussing leukemia the author does not even mention the dangers of dental extractions in this condition.

On the whole, the book is of little value to the student of medicine.

M C P

Some Factors in the Localization of Disease in the Body By HAROLD BURROWS 299 pages William Wood and Company, Baltimore, 1932 Price, \$4.50

The author discusses in this interesting monograph the present status of our knowledge concerning those factors which determine the localization in certain tissues of morbid matter carried in the blood stream. In the first part of the book he has collected under separate chapter heads what is known concerning the localization of normal and foreign proteins, of dyes and fine inorganic particles and natural pigments, of syphilis, of bacteria and viruses, and of cancer. The author has the gift of clarity of expression and he has presented the scientific data in sufficient detail so that the reader may form an independent judgment of its significance.

The nature and causes of increased capillary permeability are dealt with in Part II, the forces at play in the transport of material from the blood stream into the tissues are analyzed, and the tendency of an inflammatory process to fix colloidal and other foreign material is discussed. Many interesting data bearing on the question of local immunity are presented. Finally the author attempts to show the bearing of these principles of localization upon our therapeutic practices.

The author is a stimulating guide through a field of general pathology with which most physicians are unfamiliar. His book will re-awaken in many an interest in the fundamental mechanisms of disease.

M C P

Anleitung zur frühzeitigen Erkennung der Krebskrankheit 134 pages S. Hirzel, Leipzig, 1932 Price, Reichmark 3

This small manual was first issued in 1917 as a part of the campaign against cancer in Saxony. The present second edition has been revised by a committee including prominent names from the University clinics in Dresden and Leipzig. The book has been written for the general practitioner upon whom the success of any campaign for the early recognition of cancer depends. It should be of great assistance to him. The introductory matter is brief, consisting of short sections on cancer mortality, the general nature of cancer, diagnostic local and general signs, indications

and contraindications for operation, practical rules governing biopsy, etc. The general characteristics of cancer behavior in the chief tissue of the body, skin, mucous membrane, glands, bone, etc., are then summarized. The major portion of the book is given up to a discussion of the early cancerous lesions of each region of the body, beginning with the scalp and covering both the exterior and interior of the body.

Few small books contain as much valuable information so clearly and concisely expressed. The commoner precancerous and cancerous lesions of each region are described as to appearance and early symptoms, diagnostic findings, clinical course, and therapeutic indications. The sections read like the best type of clinical lectures, thorough, clearly organized, forceful and eminently practical.

This manual deserves careful reading by all those interested in similar campaigns in this country. It seems a model of its kind.

M C P

COLLEGE NEWS NOTES

Among gifts to the College Library of publications by members herewith acknowledged are the following

Dr Priscilla White (Fellow), Boston, Mass—1 book, "Diabetes in Childhood and Adolescence",

Dr Hyman I Goldstein (Associate), Camden, N J—1 reprint,

Dr Louis I Kramer (Associate), Providence, R I—2 reprints,

Dr Marjorie E Reed (Associate), Plymouth, Pa—2 reprints,

Dr Karl Rothschild (Fellow), New Brunswick, N J—2 reprints,

Dr Walter M Simpson (Fellow), Dayton, Ohio—4 reprints

Dr Edwin W Gehring, Fellow and Governor of the College for Maine, has been named President-elect of the Maine Medical Association for the coming year

Dr Francis B Johnson (Fellow), Professor of Clinical Pathology of the Medical College of the State of South Carolina, Charleston, was recently elected President of the Tri-State Medical Association of the Carolinas and Virginia

Dr George C Bower (Associate) has left the State Hospital at Willard, N Y, to accept a promotion as first-grade pathologist at the State Hospital at Marcy, N Y

Major E C Odom (Fellow) has completed four years of duty at the Walter Reed General Hospital, Washington, D C, and has now been transferred to the Letterman General Hospital, San Francisco

Dr Gerald B Webb (Fellow), Colorado Springs, was elected President of the Colorado State Board of Medical Examiners on July 11

Dr Janvier W Lindsay (Fellow) and Admiral Cary T Grayson (Associate) have been put in charge of the Pathologic Laboratory and the Warwick Clinic, respectively, of the Garfield Memorial Hospital. The radiologic department of this Hospital has been enlarged through the establishment of the Warwick Clinic, a bequest of the late Randolph T Warwick. The bequest provided for the establishment of an institute "for the care and treatment of women afflicted with cancer"

Dr George R Minot (Fellow), Professor of Medicine of the Harvard University Medical School, Boston, was recently awarded the Moxon gold medal of the Royal College of Physicians of England

Dr Lewis J Moorman (Fellow), Oklahoma City, succeeded to the Superintendency of the State University Hospitals, Oklahoma City

Dr G Bruce Lemmon (Fellow) has been appointed Consultant in Internal Medicine at the Federal Hospital for Defective Delinquents. This hospital, which has just been completed at Springfield, Missouri, has 705 beds and cost over \$2,000,000. Dr Lawrence Kolb (Fellow) of the U S Public Health Service is its superintendent. The institution will be known as the Medical Center for the Department of Justice and is the first of its kind

OBITUARIES

DR EDWARD OSGOOD OTIS

On May 28, 1933, Dr Edward Osgood Otis died in his eighty-fifth year. At the time of his death Dr Otis was a Governor for the American College of Physicians for New Hampshire. He had previously been a Governor for the College for Massachusetts but he had retired from active practice and had gone to live at Exeter, New Hampshire. Dr Otis had been a Fellow of the American College of Physicians since 1920 and was the oldest member in respect to age of the College. Throughout his membership Dr Otis had taken a very active interest in the College. He was one of those long, lean Yankees who never look their age and who are active physically and mentally until the end. It was with great regret that Dr Otis was obliged to forego attendance at the meeting of the College in Montreal. Although he maintained his residence for the last few years in Exeter, New Hampshire, he came frequently to Boston to attend meetings and to lend his presence to important occasions.

Dr Otis was born in 1848 at Rye, New Hampshire, went to Phillips Exeter Academy, received his bachelor degree at Harvard in 1871 and his medical degree also at Harvard in 1877. After an internship at the Boston City Hospital he took postgraduate work in Vienna. On his return he established an office in Boston and devoted himself from the beginning to diseases of the chest. In those days that meant largely tuberculosis. For 45 years Dr Otis was associated with the Boston Dispensary and in his chest clinic there he gave instruction to the medical students. For many years he was professor of pulmonary diseases and climatology at Tufts College Medical School. Tufts College gave him the honorary degree of Doctor of Sciences which the University of his native state of New Hampshire also conferred upon him.

Dr Otis acquired a very distinguished position in the practice of medicine in the city of Boston, particularly, of course, in regard to tuberculosis and other chronic diseases of the chest. He was instrumental in all activities in regard to tuberculosis. For years he was a visiting and consultant physician for the Massachusetts State Sanatorium at Rutland which was the first state institution for the early care of tuberculosis. He was a director of the National Tuberculosis Association. He had been president of the Massachusetts Tuberculosis League and President of the Boston Tuberculosis Association. He was an early member and ex-president of the American Climatological and Clinical Association and he contributed many articles and papers to the current medical journals. He was the author of "Pulmonary Tuberculosis" and "Tuberculosis—Its Cause, Cure and Prevention." Dr Otis had watched the development of internal medicine and of his specialty, tuberculosis, from its very beginnings as a science to its present state. In that rapid progress of internal medicine and of knowledge concerning tuberculosis which left so many of his generation

behind he was always in the forefront, one of the leaders His was a shrewd and cautious nature which did not run to fads but which could become enthusiastic over developments while they were still new The Yankee twang in his speech was a guarantee of his horse sense, and his apparently stern exterior covered great warmth of affection and intense personal loyalty

ROGER I LEE, M D , F A C P ,
Governor of the College
for Massachusetts

DR RAYMOND JOSEPH HARRIS

Dr Raymond Joseph Harris was born in Philadelphia in 1872 and educated in the public schools there, graduating from the Central High School with the degrees of A B and A M He matriculated in the Hahnemann Medical College of Philadelphia, graduating in 1894 From 1895 to 1902 Dr Harris served as Demonstrator of Chemistry at his Alma Mater For a number of years he was Associate Physician at the Broad Street Hospital, Philadelphia

Dr Harris died suddenly August 9, 1933, as a result of a coronary thrombosis

E J G BEARDSLEY, M D , F A C P ,
Governor of the College
for (Eastern) Pennsylvania

DR SHANNON LAURIE VAN VALZAH

Born September 18, 1888, B A , University of Oregon, 1910, M D , Johns Hopkins University Medical School, 1914, Postgraduate work in Tropical Medicine, Bacteriology, Hygiene and Military Science, Army Medical School, October 1916, to March 1917, entered the Medical Corps as First Lieutenant in 1917 and was promoted to Major in 1918, Assistant and Laboratory Officer, Fitzsimons General Hospital, 1922-24, Assistant Chief of Medical Service, Fitzsimons General Hospital 1926-33, member, Johns Hopkins Medical and Surgical Society and Association of Military Surgeons, Fellow, American Medical Association and American College of Physicians, died July 9, 1933, of diverticulitis of the sigmoid and peritonitis

Major Van Valzah entered the Medical Corps of the U S Army in 1917 during the World War, did service in France with great credit to the Medical Corps and himself After his return to the United States, while on duty at an eastern station, he developed pulmonary tuberculosis, and in 1922 was sent as a patient to Fitzsimons General Hospital, where he remained as a patient until 1923, when he was assigned to duty at that hospital His outstanding ability soon became manifest and he was detailed as Assistant to the Chief of the Medical Service and in charge of electrocardio-

graphy This position he filled with great credit until his death, at Fitzsimons General Hospital, Denver, Colorado

Major Van Valzah, had, for some years, come to consider Denver his home and planned to live there on retirement from active service from the Army He was one of those lovable individuals whose conduct was marked by kindness and consideration for others His conferees loved him for himself, respected and admired him for his professional ability and knowledge His friends both professional and lay were legion

He was married in 1916 to Miss Ola Summers of Baltimore who survives him—a charming and devoted wife who has lost a kind and loving husband The Army has lost a beloved Physician and Officer

A C COOPER, M D , F A C P ,
Lt Col , Medical Corps,
U S Army

Refined



NATIONAL DIPHTHERIA TOXOID

(Diphtheria Toxoid, Alum Precipitated)

Refined Diphtheria Toxoid is prepared from a previously standardized toxin detoxified with formaldehyde, the active antigenic substances are precipitated with aluminum-potassium sulphate, the precipitate repeatedly washed and suspended in normal saline

The immunizing (protective) value of the Refined Toxoid is determined by the amount of antitoxic units developed by one human dose, of 1 cc, of the Toxoid, given subcutaneously to guinea pigs the single dose of Toxoid must produce at least two diphtheria antitoxic units per cc of blood serum at the end of six weeks

A single dose gives prompt protection against diphtheria, in from 90 to 98 per cent of young children, with practically no local or systemic reactions

Refined Diphtheria Toxoid is furnished to physicians in ampoule vials

One Immunizing Dose, 1 cc, \$1 00	Code Word TOPA
Five Immunizing Doses, 5 cc, \$1 75	" " TOPE
Ten Immunizing Doses, 10 cc, \$3 00	" " TOPI

THE NATIONAL DRUG COMPANY
PHILADELPHIA
U.S.A.



Send

pkgs

Refined Diphtheria Toxoid per adv. in

USE CODE WORD
Annals of Internal Medicine

Name

Date

Address

State

THE POTTENGER SANATORIUM AND CLINIC FOR DISEASES OF THE CHEST

Monrovia, California



THIRTY YEARS' EXPERIENCE IN THE TREATMENT OF TUBERCULOSIS

LOCATION

Sixteen miles east of Los Angeles In the foothills of the Sierra Madre Mountains, at an elevation of 1000 feet On the main line of Santa Fe Railway Connected with Los Angeles by interurban railway and splendid boulevards

ENVIRONS

The grounds consist of a beautiful park of forty acres, in which are found a variety of native Live Oaks, subtropical trees and plants, and a profusion of beautiful shrubs and flowers Many winding walks and nooks of exquisite beauty add to its attractiveness When on exercise, patients also enjoy the beautiful trails in the adjoining canyons and mountains

MEDICAL CARE

Competent resident staff Examinations for comparison every six weeks Close medical supervision Patients visited twice daily Their individual needs and problems receive personal attention

THERAPEUTIC CARE

Fads are not followed, but an endeavor is made to give patients the amount of rest and exercise suited to their individual needs, the benefits of a liberal and adequate diet, such tonic measures as will increase their resistance, and other measures that will help them overcome any disturbing symptoms or complications that may arise Heliotherapy, tuberculin, pneumothorax and surgery employed whenever indicated

DIAGNOSTIC CLINIC

A diagnostic clinic is maintained for the study of all diseases of the chest Weekly rates from \$30 up, including medical attention, medicines (except expensive remedies) and general nursing Extra charge for operative measures (except pneumothorax)

F M POTTENGER, M D, Medical Director

For Particulars Address

THE POTTENGER SANATORIUM, Monrovia, California

THE ANALYSIS SHOWS

THE VALUABLE ALKALINE CHARACTER OF

VICHY CÉLESTINS

Natural Mineral Water

INDICATIONS

In stomach and
liver affections
and digestive disorders
in general;
in gout, arthritis
associated with uric
acidemia, uricemia,
and nephrolithiasis of
uric acid origin.



BOTTLED
AT THE SPRING
VICHY, FRANCE

ANALYSIS (GRAMS PER LITER)

Sodium bicarbonate	3 3090
Potassium bicarbonate	0 2490
Lithium bicarbonate	0 0281
Calcium bicarbonate	0.7400
Magnesium bicarbonate	0 1016
Ferrous bicarbonate	0.0012
Sodium chloride	0 3830
Sodium sulphate	0 2430
Silica	0.0300
Sodium arsenate, Phosphate and nitrate	} present

Brochure with Therapeutic Data and Medical Bibliography
sent on request.

Sole United States Agents, American Agency of French Vichy, Inc., 503 Fifth Ave , New York

New LEA & FEBIGER Books

NEW WORK

JUST READY

DIETETICS FOR THE CLINICIAN

By MILTON ARLANDEN BRIDGES, B S, M D, F A C P.

Associate in Medicine at the New York Post-Graduate Medical School, Columbia University, New York

IN COLLABORATION WITH

RUTH LOTHROP GALLUP

Dietitian

WITH A FOREWORD BY

HERMAN O MOSENTHAL, A B, M D

Director of Medicine at the New York Post-Graduate Medical School, Columbia University, New York

Octavo, 666 pages Cloth, \$6 50, net

This book is designed to fill the great need for a work on dietary management which is readily understandable and from which practice can be immediately instituted. It is written for the general practitioner and the hospital interne, and it should commend itself to the dietetic department of every hospital and clinic. It is a handbook for the worker in the field of medicine who does not have the more detailed treatises at his immediate disposal. The author has reviewed the entire literature of the field at large and has produced an assimilation of the various dietetic tables. The material here offered is not only physiologically sound and essentially practical, but has been adjusted to the physician and his patient.

INTERNAL MEDICINE

ITS THEORY AND PRACTICE

In Contributions by American Authors

Edited by JOHN H MUSSER, B S, M D, F A C P.

Professor of Medicine in The Tulane University of Louisiana School of Medicine, Senior Visiting Physician to the Charity Hospital, New Orleans, Louisiana

Octavo, 1316 pages, illustrated. Cloth, \$10 00, net

This book is the work of twenty-seven recognized authorities, each of whom holds a professorial appointment in a prominent medical school. Each covers that sub-division of internal medicine in which he is particularly qualified, each writes from the viewpoint of his experience as a teacher and presents his specialized knowledge in such a way as to make the work an authoritative source of information to the student. The book is well organized, without repetitions, concise but comprehensive.

CALCIUM METABOLISM AND CALCIUM THERAPY

By ABRAHAM CANTAROW, M D.

Instructor in Medicine, Jefferson Medical College, in Charge of Laboratory of Biochemistry, Jefferson Hospital, Assistant Physician, Philadelphia General Hospital

WITH A FOREWORD BY

HOBART AMORY HARE, B Sc, M D, LL D

Late Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College, Philadelphia

NEW (2nd) EDITION 12mo, 252 pages, illustrated, limp binding, \$2 50, net

The discovery of the antirachitic factor and the parathyroid hormone resulted in the rapid development of this field, reflected in the accumulation of a voluminous literature. Ten years ago hardly any of the now well-established principles could have been presented, even speculatively. This work has kept pace with the rapidly accumulating knowledge and established calcium therapy on a rational basis.

LEA & FEBIGER

Please send me books checked

☐ Bridges - - - - - \$ 6 50
☐ Musser - - - - - 10 00



☐ Cantarow - - - - - 2.50
☐ New Catalogue

600 Washington Square
PHILADELPHIA, PA.

Name _____
(A. of L. 11-33)

Address _____

BOOKS

FOR THE PHYSICIAN'S LIBRARY

Adler's CLINICAL PHYSIOLOGY OF THE EYE	\$5 00	Horgan's RECONSTRUCTION OF THE BILIARY TRACT	\$4 00
Anderson's DETACHMENT OF THE RETINA	\$4 50	Humphris' PHYSIOTHERAPY	\$4 50
Barclay's THE DIGESTIVE TRACT	\$12 00	Huxley's ELEMENTS OF EXPERIMENTAL EMBRYOL- OGY	Preparing
Baur-Fisher-Lenz' HUMAN HEREDITY	\$8 00	James' HISTORY OF OPHTHALMOLOGY IN ENGLAND	\$4 00
Bloomfield-Polland's GASTRIC ANACIDITY	\$2 50	Knox' X-RAY THERAPEUTICS	\$7 00
Cameron's TEXTBOOK OF BIOCHEMISTRY, 4th ed	\$3 75	Landman's HUMAN STERILIZATION	\$4 00
Capps' PAIN IN THE PLEURA, PERICARDIUM AND PERITONEUM	\$3 00	Lewis' DISEASES OF THE HEART	\$3 50
Clifford's THE SPUTUM	\$4 00	Needham's CHEMICAL EMBRYOLOGY	\$26 50
Cowdry's ARTERIOSCLEROSIS	\$5 00	Osgood-Allison's FUNDAMENTALS OF ORTHOPAEDIC SURGERY	\$3 00
Dawson's HISTORY OF MEDICINE	\$2 50	Rackemann's CLINICAL ALLERGY	\$7 50
Dixon's THE MANO-METRIC METHODS FOR MEAS- URING CELL RESPIRATION	Preparing	Rasmussen's PRINCIPAL NERVOUS PATHWAYS	\$2 50
Doll-Phelps-Melcher's MENTAL DEFICIENCY DUE TO BIRTH IN- JURIES	\$4 50	Rockwell's STREPTOCOCCIC BLOOD STREAM INFECTIONS	\$1 75
Emerson's ALCOHOL AND MAN	\$3 50	Stephen's PSYCHOANALYSIS AND MEDICINE	\$2 50
Fisher's INTERNAL DERANGEMENTS OF THE KNEE- JOINT	\$3 50	Stern's CLINICAL DIAGNOSIS PHYSICAL AND DIF- FERENTIAL	\$3 50
Friedenwald's PATHOLOGY OF THE EYE	\$3 50	Stryker's COURTS AND DOCTORS	\$2 00
Harrison's CHEMICAL METHODS IN CLINICAL MEDI- CINE	\$5.25	White's HEART DISEASE	\$7 50
Holmes' CANCER AND SCIENTIFIC RESEARCH	\$1 50	Wilson's FRACTURES AND THEIR COMPLICATIONS	\$10 50
		Zinsser's RESISTANCE TO INFECTIOUS DISEASES	\$5 00

THE MACMILLAN COMPANY

60 FIFTH AVENUE

PUBLISHERS

NEW YORK

Bromural

Alphabromisovalerylcarbamide

Council Accepted

AS A ROUTINE SEDATIVE

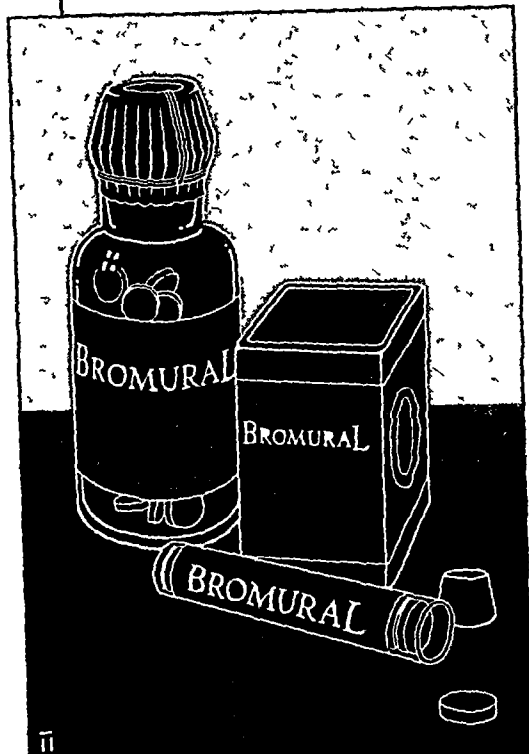
in general nervous disturbances prescribe one tablet (5 grains) several times a day. As a mild and prompt hypnotic the dose is 2 to 3 tablets upon retiring or during the night. Bromural is not a barbiturate nor a bromide.

5 grain tablets and as a powder.

Samples and literature upon request

Bilhuber-Knoll Corp.,

154 Ogden Avenue, JERSEY CITY, N. J.



*...There is a reason why
Pil. Digitalis (Davies,
Rose) have become the
choice of Cardiologists*

... They are digitalis in its completeness—physiologically tested leaves in the form of physiologically standardized pills, giving double assurance of dependability

Each pill contains 0.1 gram, the equivalent of about 1½ grains of the leaf, or 15 minims of the tincture

Convenient, uniform, and more accurate than tincture drops.

Sample and literature upon request

DAVIES, ROSE & CO., Ltd.

Pharmaceutical Manufacturers,

BOSTON, MASS.



Devitt's Camp, Inc.

ALLENWOOD
PENNSYLVANIA

(Tuberculosis)

*On beautiful White Deer Mountain, 20 miles southeast
of Williamsport, Pa.*

All modern methods of treatment, including heliotherapy, artificial pneumothorax, phrenic exaeresis, Jacobaeus operation, and thoracoplasty

Not operated for profit Moderate rates Modern buildings

Patients given individual attention by experienced physicians and specially trained registered nurses

The following physicians will be glad to examine patients for admittance to Camp

J M ANDERS, M D, Philadelphia, Pa
ISABEL M BALPH, M D, Philadelphia, Pa
E J G BEARDSLEY, M D, Philadelphia, Pa
WARD BRINTON, M D, Philadelphia, Pa
F W J BURGE, M D, Philadelphia, Pa
DAVID A COOPER, M D, Philadelphia, Pa
DONALD R FERGUSON, M D, Philadelphia, Pa
JOHN B FLICK, M D, Philadelphia, Pa
JOHN A KOLMER, M D, Philadelphia, Pa
W ESTELL LEE, M D, Philadelphia, Pa
A C MORGAN, M D, Philadelphia, Pa
ARTHUR W PHILLIPS, M D, Philadelphia, Pa
GEO MORRIS PIERSOL, M D, Philadelphia, Pa
EDWARD R SNADER, Jr, M D, Philadelphia, Pa
MERVYN R TAYLOR, M D, Philadelphia, Pa
THOS J VISCHER, M D, Philadelphia, Pa
A S KECH, M D, Altoona, Pa
CHARLES C HABLSTON, M D, Baltimore, Md
CHARLES S AITKEN, M D, Brookline, Pa.
J C ATWELL, M D, Butler, Pa
F DECARIO, M D, Bradford, Pa
J W WOOD, M D, Chester, Pa

JOHN E FRETZ, M D, Easton, Pa
RICHARD R DALRYMPLE, M D, Erie, Pa
JESSE L LENKER, M D, Harrisburg, Pa
H B ANDERSON, M D, Johnstown, Pa
JOHN H ESBENSHADE, M D, Lancaster, Pa
E J WERLE, M D, Meadville, Pa.
CHARLES G CRANE, M D, Newark, N J
W A WOMER, M D, New Castle, Pa.
EDWARD S MCSWEENEY, M D, New York City
M THERESA SCANLAN, M D, New York City
STANLEY L WANG, M D, New York City
W R GLENNEY, M D, Pottsville, Pa
R. R JONES, M D, Pittsburgh, Pa
C L PALMER, M D, Pittsburgh, Pa
A H COLWELL, M D, Pittsburgh, Pa
HOWARD U MILLER, M D, Reading, Pa
A E DAVIS, M D, Scranton, Pa
H D WILLIAMS, M D, Trenton, N J
B M ALLEN, M D, Wilmington, Del
JOHN MINOR, M D, Washington, D C
J W PEABODY, M D, Washington, D C
H R SCHREIBER, M D, Washington, D C
E W BIXBY, M D, Wilkes Barre, Pa
HARRY M READ, M D, York, Pa

BOOKLET

ROSS K CHILDERHOSE, M D
JOHN S PACKARD, M D
Associate Physicians

WILLIAM DEVITT, M D
*Superintendent and
Physician in Charge*

One of a series of advertisements prepared and published by Parke, Davis & Co. in behalf of the medical profession. This 'See Your Doctor' campaign is running in the *Saturday Evening Post* and other leading magazines.



"Things I wish my Mother hadn't taught me"

VERY young woman who embarks upon the great adventure of Motherhood is overwhelmed with advice from those who love her most.

The advice may be on some apparently trivial matter—clothing, feeding, what to do for an upset stomach, or the way to nip a cold in the bud.

Yet many a brand-new mother has learned that often the reward for following such advice is regret. She has said, not in bitterness, but in sadness, "I wish I had never been told to do that." She has learned, too late, that many of the beliefs of a generation ago have been cast into disrepute by the findings of recent years.

For these past few decades have been a Golden Age of Medicine. Much has been learned, much has been disproved. And, as a result of developments and discoveries that

have taken place since you yourself graduated from childhood, the baby of today has a better chance of arriving into the world safely, of successfully weathering the treacherous storms of infancy, and of enjoying a healthy, vigorous childhood.

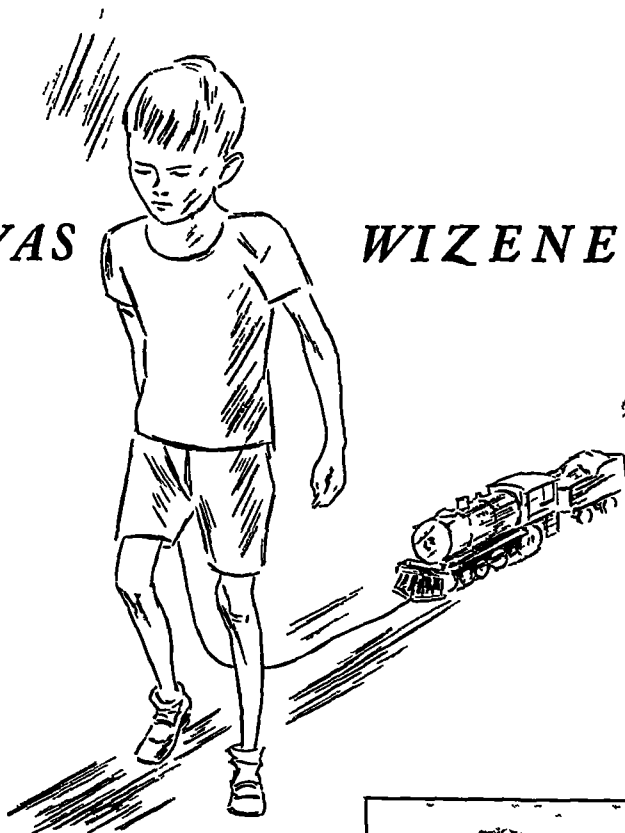
A better chance, that is, if medical science is given the opportunity of exerting its influence on the child and on the mother. It is difficult not to take advice from those who love us most. But when so fragile and precious a thing as a baby's health is at stake, there is one person, and one person only, whose advice you can safely follow.

That person is your doctor.

PARKE, DAVIS & COMPANY

*The World's Largest Makers
of Pharmaceutical and Biological Products*

JIMMY WAS WIZENED



HE was a Doctor's kid, given every possible care. One day, after Dr. Dad listened to his heart, Jimmy made the rounds of well-known pediatricians. He was unanimously condemned to inactivity.

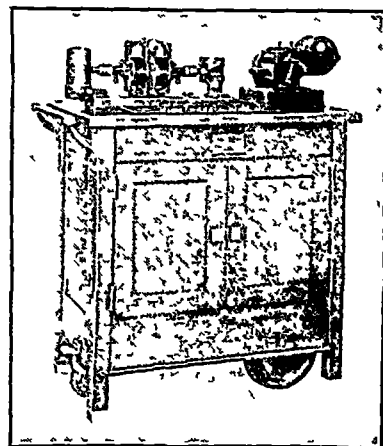
Yes, Jimmy became wizened from lack of exercise and air. Luckily there was a competent cardiologist among his father's friends. Six months after the start of Jimmy's sentence, this cardiologist was consulted and he took tracings with his "Hindle" Electrocardiograph. The heart muscle proved to be in good condition even though abnormal sounds were heard. Since then activity and sunshine have done their work. Today Jimmy is not wizened.

This is a true happening and its use for an advertisement was suggested by grateful Dr. Dad. Complete facts will be gladly given to interested doctors.

"Pioneer Manufacturers of the Electrocardiograph"

**CAMBRIDGE
INSTRUMENT CO. INC.**

3732 Grand Central Terminal
New York City

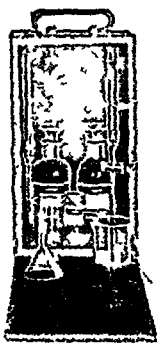


The Hindle "all-electrics" operate directly from the lighting system. They are characterized by their accuracy, dependability, ruggedness and simplicity of operation. Ideal for use in hospitals, clinics or private offices.

Send for Literature

H I N D L E
"ALL-ELECTRIC"
ELECTROCARDIOGRAPH

LaMOTTE Blood Urea Outfit



For study of urea retention (urea nitrogen by factor)

Result is read directly from special Urea Burette supplied

No calculations required
Accurate to 4 mg urea per 100 cc blood

Complete estimation takes only 15 to 20 minutes

Price, complete with instructions, \$18.50 f.o.b. Baltimore, Md

Your LaMotte Blood Chemistry Handbook* illustrates and describes many other simple, accurate testing outfits developed by LaMotte Research Department in co-operation with recognized specialists

*If you do not have one, write today for a complimentary copy

LaMOTTE Chemical Products Co.

418 Light Street

Baltimore, Md.

CURDOLAC FOODS LENGTHEN DIABETIC LIVES

Blood sugar producing properties are low because these foods are.

1. Moderate in carbohydrate content, yet
2. Not excessive in protein and fat.

(58% of the protein and 10% of the fat consumed produce sugar in the blood)

Samples and literature on request

CURDOLAC FOOD CO.

Box 299

Waukesha, Wis.

A Present to Yourself at Christmas



Fellowship Key

A charm, bearing the seal of the American College of Physicians, wrought in solid gold and embossed in the College colors, engraved on reverse side with initials and date of election. For Fellows only. Price, \$7.00, postpaid.

Available also in lapel button or fraternity pin with safety catch, \$4.00, postpaid.



Fellowship Pledge

A beautiful engraved and framed parchment of the official Fellowship Pledge, taken at time of induction. Space for your signature beside the College seal. Suitable for office or reception room. Price, \$6.00, postpaid.



AMERICAN COLLEGE OF PHYSICIANS

133-35 S. 36th St. Philadelphia, Pa.

DIGITALIS THERAPY DEMANDS UNIFORMITY

THE increasing use of the Lederle Tablets of Digitalis is an indication that physicians treating cardiac disturbances have found them uniform, stable and accurately standardized

The Lederle Tablets of Digitalis were perfected as a result of six years' experience in the Cardiac Clinics of Greater New York with tablets of standardized digitalis leaf having a potency of 1 cat unit in $1\frac{1}{2}$ grains of powdered leaf

Only digitalis leaf which has been clinically demonstrated to possess *uniform activity*, is used in the preparation of the Lederle Digitalis Tablets

The intravenous method of Hatcher and Brody used by the Lederle Laboratories directly measures the cardiac effects of the drug

Since neither the intravenous Cat Method nor the official One Hour Frog Method measure the absorption of digitalis in man, the Lederle leaf is clinically tested in cardiac cases before any is used in the preparation of the Lederle Tablets.

The uniformity of the Lederle Tablets is maintained by a careful blending of the powdered leaf. When 10% of the original stock has been used, a like amount of carefully selected standardized leaf is added. Thus there can be at no time any appreciable variation in the clinical results. This is the method developed by the Cardiac Clinics of Greater New York which are controlled by the Heart Committee of the New York Tuberculosis and Health Association.

Digitalis Tablets Lederle are supplied in packages containing 100 tablets (5 tubes of 20), in three sizes: $\frac{1}{2}$ Cat Unit ($\frac{3}{4}$ grains*) 1 Cat Unit ($1\frac{1}{2}$ grains*) 2 Cat Units (3 grains*)

*The comparison of the cat unit of digitalis to the grain of powdered digitalis leaf refers to the leaf selected as described above for the Lederle product, namely, that one and one-half grains of the powdered leaf assay one cat unit. In the above table, grains are stated only as an approximate guide to the physician who has heretofore based his dosage on weight or volume.

Literature and samples to Physicians upon request



LEDERLE LABORATORIES, INC
NEW YORK



Calm Sleep - Bright Awakening

To the patient exhausted by persistent insomnia, restful and refreshing sleep is a tonic both to mind and body

In the common types of nervous insomnia, the administration of Phanodorn is followed by sleep closely approximating the normal. There is no harmful effect on respiration or cardiac function. After an adequate period of sound sleep the patient usually awakens without a hangover of drowsiness, dulness, headache, dizziness.

An increasing number of physicians are adopting Phanodorn as the hypnotic of choice for everyday practice. Its field of indications includes insomnia associated with neurasthenia and other neuroses as well as sleeplessness during the course of acute and chronic organic diseases.

DOSE: .1 tablet at bedtime, preferably with warm drink, increased to 2 tablets in obstinate insomnia.

Sample and literature on the action and therapeutic indications of Phanodorn will be sent to physicians on request.

PHANODORN

Trademark Reg. U. S. Pat. Off.

Brand of CYCLOBARBITAL



Supplied in 3 grain tablets, tubes of 10 and bottles of 100



WINTHROP CHEMICAL COMPANY, INC., NEW YORK, N. Y.
Laboratories and Factory Rensselaer, N. Y.

TWO FUNDAMENTALS IN THE TREATMENT OF DIABETES . . .

Insulin ... *Diet*

As we know, the diet will vary with the needs of the individual patient

But the Insulin should always be a constant, unvarying, dependable therapeutic agent

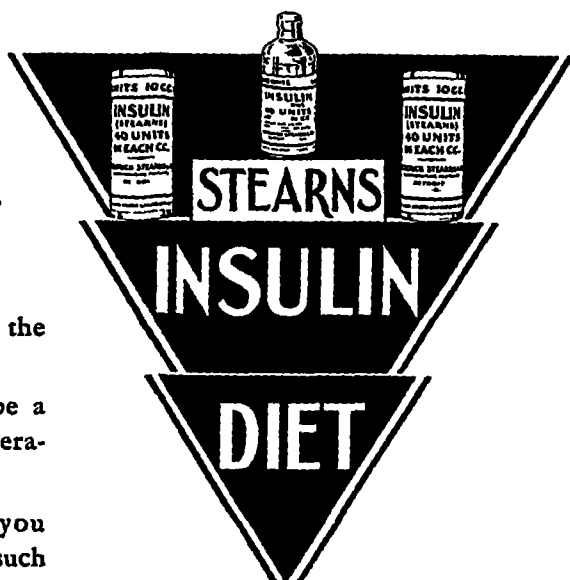
When you use Insulin-Stearns, you know that it is prepared under such exacting conditions of laboratory manufacture that it is

Biologically exact in potency

Remarkably clear

Notably free from sting
at point of injection

We take the utmost pride in the efficiency of our Insulin department with its modern equipment and its scientific



personnel, and we are only too glad to demonstrate the step-by-step process of manufacture to interested physician visitors

Let us send you complete literature describing Insulin-Stearns—how it is made, how it is supplied and recommended for use in actual practice. The facilities of Stearns Insulin Research Department are always at your service

FREDERICK STEARNS & COMPANY
DETROIT, MICHIGAN, U. S. A.

FREDERICK STEARNS & COMPANY
Detroit, Michigan

AIM 11

Gentlemen I will be glad to have complete literature describing Insulin-Stearns

Doctor . . .

Address . . .

City . . .

State . . .



Both Assay and Dosage Under Greater Control

WYETH'S CAPSULES DIGITALIS LEAF (DEFATTED)

For the greater protection of you and your patient, Wyeth's Capsules Digitalis Leaf (Defatted) is checked and double checked by TWO methods of standardization



Both the U S P. frog method and the cat unit method of Hatcher and Brody are employed on every batch—only those batches which give concordant results are passed as satisfactory for clinical use

In this way greater accuracy of dosage can be expected

Furthermore, each capsule contains an unvarying quantity of this more accurately standardized drug.

No dropper or measuring device is used by you or your patient, thereby eliminating another possible source of error.

Wyeth's Capsules Digitalis Leaf (Defatted) is supplied in vials of 36 and 100 distinctive green capsules

If you have not already had an opportunity to submit Wyeth's Digitalis to test, we will be glad to send you an original package with our compliments

Control the integrity of your prescriptions
by specifying Wyeth's pharmaceuticals.

JOHN WYETH & BROTHER, INC.
PHILADELPHIA, PA. and WALKERVILLE, ONT.



The Functions of Vitamin A in the Diet

"DIETARIES deficient in Vitamin A lessen the vigor of the body and its ability to resist disease, and, as a result of such weakening there develops an increased susceptibility, so that the incidence of any number of diseases (of which tuberculosis serves as an outstanding example) *may be largely influenced by the adequacies of the diet as regards Vitamin A*" *

While it has long been known that general vigor, as represented by growth, is influenced by Vitamin A, recent studies show that this substance also possesses anti-infective properties as well. Vitamin A, therefore, is not only important in promoting growth, but, on the basis of experimental evidence, also seems to be important in building up bodily resistance to infection—particularly of the respiratory system. Such

resistance is all the more essential in view of the more serious diseases often resulting from colds.

The administration of vitamins, like the prescription of medicine, should be solely the prerogative of the physician. Some vitamins are held to exhibit a marked sympathetic unity. For this reason it seems desirable to administer them in one nutritious combination. In addition to Vitamin A, Maltine With Cod Liver Oil also contains Vitamins B (b_1), G (b_2) and D. Taken with orange or tomato juice Vitamin C is added, thus providing five vitamins.

Maltine With Cod Liver Oil is being widely prescribed by physicians because of its known vitamin potency and because of the eminently satisfactory results following its administration. Maltine with Cod Liver Oil is biologically standardized and guaranteed to contain four different vitamins—A, B (b_1), G (b_2) and D. Biological report on request. The Maltine Company, *Est* 1875, 30 Vesey Street, New York, N. Y.

* Sherman & Smith—The Vitamins—1931 Ed. Pg. 287



THE ORIGINAL

Maltine

WITH COD LIVER OIL

Introduced in 1875

Please Mention this Journal when writing to Advertisers



COUNCIL ACCEPTED



economical for vitamin **A**

MEAD'S HALIBUT LIVER OIL

(Without Viosterol)

32,000 U.S.P. Vitamin A Units and 200 Steenbock Vitamin D Units per gram. 10 cc. and 50 cc. bottles.*

economical for vitamin **D**

MEAD'S VIOSTEROL IN OIL 250 D

(Contains No Vitamin A)

3,333 Steenbock Vitamin D Units per gram. 5 cc. and 50 cc. bottles.

economical for vitamins **A and D**

MEAD'S VIOSTEROL IN HALIBUT LIVER OIL 250 D

32,000 U.S.P. Vitamin A Units and 3,333 Steenbock Vitamin D Units per gram. 5 cc. and 50 cc. bottles.

*brown bottles in light-proof cartons to protect against deteriorating action of light, supplied with combination dropper-stopper

MEAD JOHNSON & CO., Evansville, Indiana, U.S.A.

These bottles are sealed with a red wax cap and are supplied with a combination dropper-stopper to cooperate in preventing their reaching unauthorized persons

Please Mention this Journal when writing to Advertisers

ANNALS OF INTERNAL MEDICINE

VOLUME 7

NOVEMBER, 1933

NUMBER 5

HEPATIC PATHOLOGY IN EXOPHTHALMIC GOITER

By CARL VERNON WELLER, M S, M D, F A C P, *Ann Arbor, Michigan*

IN A PRELIMINARY report¹ the writer has called attention to the frequent occurrence of chronic parenchymatous hepatitis in varying degrees in patients with Graves' disease. In the present paper the various lines of evidence bearing upon the coincidence of these conditions will be reviewed more completely, a somewhat more rigidly controlled series will be analyzed, and the lesions more fully described, than was possible in the earlier report.

There are four distinct avenues of approach to the problem of the nature of the interrelation between the liver and the thyroid gland, particularly as it concerns the hyperthyroid state. The gross and microscopic changes, with which the present investigation is primarily concerned, complement certain clinical, functional, and experimental observations which must first be reviewed.

I ICTERUS IN EXOPHTHALMIC GOITER

The occurrence of icterus in patients presenting otherwise the signs and symptoms of exophthalmic goiter has been noted with sufficient frequency to justify investigation of this point. It must be recognized, as Lichtman² has recently emphasized, that in such cases the icterus may be an unrelated condition, and as such may be due to cholelithiasis, catarrhal jaundice, cholangitis, syphilis, or to any other of the various recognized causes. Also, icterus in exophthalmic goiter may be due to circulatory changes in the liver, associated with cardiac decompensation, thus bringing the liver condition into a somewhat remote relationship to the thyroid but without implying any specific etiological connection between the two. The frequency with which icterus is mentioned in case reports of exophthalmic goiter suggests that these two groups alone are inadequate to explain all examples and that a toxic action on liver tissue may be present.

Habershon³ (1874) noted the occurrence of jaundice in a patient with exophthalmic goiter, appearing 10 days before death and increasing markedly. As if to rule out the possibility that it might be due to chronic passive

* Presented at the Sixteenth Annual Clinical Session of the American College of Physicians, San Francisco, California, April 5, 1932.

From the Department of Pathology, University of Michigan, Ann Arbor, Michigan.

congestion, he stated that the liver "was of a bright-yellow color, anemic, and in no way nutmegged" Eger,⁴ in 1880, observed icterus of the skin and conjunctiva in morbus Basedowni. The liver of this patient had a saffron-yellow parenchyma, perhaps largely because of lipoidosis, when it was seen at autopsy. Sutcliff⁵ (1898) found slight jaundice present in "an extraordinarily acute case of Graves' disease." Three cases of jaundice occurring in persons suffering from exophthalmic goiter were described by Eder⁶ in 1906. The third case can be discredited, since there was a history of cholelithiasis, but in the first there was no cardiac enlargement, and in the second the jaundice improved, although certain cardiac symptoms which were present remained unchanged. An extensive survey of the reported occurrence of icterus in exophthalmic goiter prior to 1908 is given by Sattler.⁷

Such observations as these have occurred sufficiently frequently to justify certain clinical generalizations which can be found among the more complete descriptions of exophthalmic goiter. Thus Boothby⁸ wrote of the "tendency to gastrointestinal crises of nausea, vomiting and diarrhea, with jaundice as a frequent terminal condition in cases of long duration," and also "Jaundice is not an infrequent accompaniment of the late stage of a long continued, gastrointestinal, thyroid crisis and is distinctly a dangerous sign. In most instances it seems to be an integral part of the syndrome and due directly to the thyroid intoxication. In all probability it is only rarely due directly to cholelithiasis or an independent biliary infection, although such conditions, if present, may be lighted up and rendered acute." Similarly, Crotti⁹ may be quoted "In a few cases of very severe thyrotoxicosis, icterus may be observed. This icterus is rare, although it is not uncommon to observe a yellowish tint of the sclerotics in severe thyrotoxic gastrointestinal disturbances. The prognosis of this icterus is always bad."

Heilmeyer¹⁰ found that among 101 cases of exophthalmic goiter in his own clinic, six showed icterus that could not be explained upon any other basis. These were usually the more severe cases and one proved fatal.

As to our own material, 35 cases were chosen from those used in the morphological section of this paper as having satisfactory histories for the investigation of this point. In eight of the 35 there was some reference to jaundice varying from slight to marked.

Various other references to the occurrence of icterus may be found in Section IV, dealing primarily with the morphological changes in the liver.

Of special interest are those cases in which the evidences of a degenerative hepatitis are so marked as to lead to a diagnosis of acute yellow atrophy. An example of this type was reported by Kerr and Rusk¹¹ in 1922. Their patient, a male, 39 years old, had presented the signs and symptoms of hyperthyroidism for a number of months. Failing appetite, nausea and vomiting were followed by deepening icterus, extreme weakness, cardiac palpitation, diminished liver dullness, bile pigment in the urine, a semicomatose state and finally convulsive movements of the extremities.

THE ANALYSIS SHOWS THE VALUABLE ALKALINE CHARACTER OF VICHY CELESTINS Natural Mineral Water

ANALYSIS
(GRAMS PER LITER)

Sodium bicarbonate	3.3090	}	Sodium bicarbonate and nitrate present
Potassium bicarbonate	0.2490		
Lithium bicarbonate	0.0281		
Calcium bicarbonate	0.7400		
Magnesium bicarbonate	0.1016		
Ferrous bicarbonate	0.0012		
Sodium chloride	0.3830		
Sodium sulphate	0.2430		
Silica	0.0300		
Sodium arsenate, phosphate and nitrate			

BOTTLED
AT THE SPRING
VICHY, FRANCE



INDICATIONS

In stomach and liver affections
and digestive disorders
in general;
in gout, arthritis
associated with uric
acidemia, uricemia,
and nephrolithiasis of
uric acid origin.

Brochure with Therapeutic Data and Medical Bibliography
sent on request.

Sole United States Agents, American Agency of French Vichy, Inc., 503 Fifth Ave., New York

California
(except expectant
pneumonia)
amount of rest and
diet: such food
as them over-
the amount
Close medical
found a variety of
drugs and have
When on exercise
the stomach at
with Los Angeles
TMENT
AND

erance These authors concluded "It is probable, therefore, that a change in thyroid activity in thyrotoxicosis may result in a glycogen free or poor liver, more susceptible to damage by some toxic agent present in this disease, or more susceptible to injury by the disturbed thyroid function itself" This conception is not necessarily in contradiction to the generalization of Pende¹⁷ (1928) to the effect that liver function in respect to urea formation, glycogen fixation and mobilization, de-aminization, cholesterol metabolism, and bile production is decreased with decreased thyroid activity and that *in Basedow's disease a condition of hyperfunction of the liver exists*

Kugelmann,¹⁸ in 1930, reviewed the rapidly increasing literature upon the disturbances in carbohydrate metabolism in exophthalmic goiter and reported the results of further studies of the blood sugar curves of normal and exophthalmic individuals following the feeding of levulose He concluded that the thyrotoxic liver not only suffers severely as a depot for stored glycogen, but also has lost the capacity to transpose large amounts of levulose to dextrose and to store it Thus the functional disturbance includes an intermediary phase in carbohydrate metabolism

So constant are the changes in carbohydrate metabolism in exophthalmic goiter as evidenced by the discharge of glycogen from the liver, that this reaction has been made the basis of a biological test for thyroxin¹⁹ and for hyperthyroidism,²⁰ using the liver of the mouse as the test object Himmelberger²¹ modified the technic of the mouse test and showed that the urine as well as the blood serum of patients with Graves' disease contains a substance capable of disturbing liver function when injected into mice

In other respects, as well, there is evidence of disturbed liver function in patients with Graves' disease Heilmeyer¹⁰ (1931) found the urobilin quotient (urine urobilin/stool urobilin) to be elevated in half of six cases investigated As tested by the method of v Bergmann and Eilbott, the bilirubin-eliminating power of the liver was impaired in each of a group of five cases This he believed to be due to a toxic injury of the liver dependent upon the thyroid hormone, and not to circulatory insufficiency

Lichtman² found that the galactose tolerance test gave no indication of a disturbance of hepatic function in a series of patients with uncomplicated hyperthyroidism Likewise, he found little evidence of appreciable disturbance of the excretory functions of the liver as determined by studies on the icterus index, bilirubinemia, urobilinuria and urobilinogenuria However, "a disturbance in the oxidation of cinchophen has been demonstrated in 16 of 20 cases of uncomplicated hyperthyroidism Thirteen of these cases showed an increased excretion of oxy-cinchophen in the urine up to 150 mg daily Larger amounts, between 150 and 200 mg, or from 31 to 42 per cent of the standard test dose, were excreted in the remaining three cases On the basis of previous experience, this is believed to indicate moderate impairment of the capacity of the liver cell to oxidize this substance further In no instance was severe impairment of hepatic function noted

"There was no apparent relationship between the degree of functional impairment of the liver and the basal metabolic rate, the known duration of the disease, or the percentage of weight lost. In individual cases, however, there appeared to be a tendency for the function of the liver cells to improve as the basal metabolic rate returned to normal.

"The constancy of depletion of glycogen in the liver cells in animals that have been fed thyroid substance and probably in clinical thyrotoxicosis suggests that the disturbance in oxidation of cinchophen is related to the capacity of the cells to store and mobilize glycogen."

III EVIDENCES OF HEPATIC DYSFUNCTION IN EXPERIMENTAL HYPERTHYROIDISM

In this section will be reviewed the evidence to which Lichtman referred in the quoted paragraph preceding, that which indicates an alteration in liver function in animals to which thyroid substance or thyroxin has been administered.

In 1905, Schryver²² found that the livers of thyroid-fed animals showed a greater degree of autolysis after 24 hours than those of the non-thyroid-fed control animals. However, when thyroid had been fed for eight days or more, an opposite effect was observed.

A large proportion of the studies in this field have dealt with carbohydrate metabolism. Cramer and Krause²³ showed in 1913, that when small amounts of fresh thyroid gland are administered for two to three days to rats or cats fed on a carbohydrate-rich diet, the liver will be found to contain only traces of glycogen. This effect they found to be due to an inhibition of the glycogenic function of the liver, and not to an increased utilization of carbohydrates. It was not accompanied by glycosuria. Parhon,²⁴ Kuriyama,²⁵ and Fukui²⁶ all found the hepatic glycogen greatly diminished in experimental hyperthyroidism. Kuriyama found that in fasted rats the liver glycogen reappeared abundantly after the ingestion of a comparatively small amount of food. If a sufficiently large amount of food were administered to thyroid-fed rats, liver glycogen might sometimes reappear to a limited extent, but the quantity of glycogen so stored was much smaller than that in fasted rats which had received food with a fuel value several times less.

With pure thyroxin, and also with liver extract, Reinwein and Singer²⁷ demonstrated an increased use of O_2 by living liver cells when these substances were applied to them in concentrations of 10^{-8} to 10^{-11} . An inhibiting effect was noted at a concentration of 10^{-5} .

Dresel, Goldner, and Himmelweit²⁸ concluded that only to a slight degree, if at all, does thyroxin have a direct effect in inciting tissue oxidation. After injection of thyroxin, split products derived from proteins appear in the liver in increased amount, and it is these, and especially tyrosin, they believe, which are responsible for the elevated rate of oxidation. With

this conclusion these authors felt that they had demonstrated a *circulus vitiosus* in that thyroxin leads to an increased output of tyrosin, and tyrosin in turn, combining with iodine in the thyroid, builds thyroxin

Under prolonged thyroid feeding other changes take place in the liver which quantitatively more than offset the loss of weight due to the lack of glycogen. This was shown by Simonds and Brandes²⁹ who rendered dogs thyrotoxic by heavy thyroid feeding for periods varying from 32 to 100 days. In these dogs the actual liver weight was in every instance greater than the theoretical liver weight as calculated for the final body weight. The mean difference was 26 per cent greater, although the mean loss of body weight was 31 per cent. In contrast, in the animals suffering from inanition, but not thyrotoxic, the actual weight of the liver was less than the calculated value with but a single exception. These authors suggested that increased functional activity and increased rate of blood flow might explain the failure of the livers of thyrotoxic animals to lose weight to the expected degree, resulting in a relative, if not an actual, hypertrophy. In this connection it may be noted that Hewitt³⁰ found that the liver was frequently hypertrophied in white rats which had received 0.1 gm. or more of fresh thyroid substance per day. These results were in accord with those of Hoskins³¹ who, two years before, had found that in thyroid-fed albino rats the liver was relatively considerably heavier than in the controls. Females showed an increase in the absolute weight of the liver of 26.7 per cent and 30.5 per cent for the older and younger groups respectively, and males showed increases of 24.4 per cent and 6.4 per cent in the corresponding groups.

IV STRUCTURAL CHANGES IN THE LIVER IN HYPERTHYROIDISM

The clinical observations of icterus in patients with exophthalmic goiter, the results of testing hepatic function in such patients, and evidences of hepatic dysfunction or hyperfunction in experimental hyperthyroidism, as reviewed in the three sections preceding, presage the occurrence of demonstrable structural changes in the liver under such circumstances. Experimental evidence of such, as well as descriptions of hepatic changes in human material, are afforded by the literature.

Hepatic Lesions in Experimental Hyperthyroidism In addition to the examples of actual or relative hypertrophy of the liver in experimental animals fed thyroid substance, as noted in the preceding section, there are but few references to changes in the liver in the experimental group. Farrant³² stated that the livers of cats and rabbits, fed thyroid gland, showed fatty degeneration, most marked around the centers of the lobules. In a study directed especially toward the heart in experimental hyperthyroidism, Hashimoto³³ found parenchymatous degeneration of the liver cells about the efferent veins, varying from "fatty degeneration" to necrosis. These changes were sometimes found throughout the lobule, but were never confined to the periphery. Hypertrophy of liver cells, mitotic figures and

double nuclei were found in the peripheral zones. While the evidences of chronic passive congestion coincided with marked myocardial changes, the parenchymatous degeneration did not.

Gross and Microscopical Changes in the Liver in Exophthalmic Goiter
In 1880, Eger⁴ gave a detailed history of a case of hyperthyroidism in which icterus of the conjunctiva and skin had been noted. At autopsy the liver was found to be atrophic, the left lobe having the appearance of being but an appendage to the right. The parenchyma was saffron-yellow grossly, and microscopically showed lipoidosis, with intact liver cells remaining only in areas. Fainer³⁴ mentioned "atrophic cirrhosis of the liver" in his Case I, and "marked atrophic cirrhosis" in Case IV. This patient showed an icteric coloration of the skin and body fluids. Cirrhosis hepatis was recorded by Askanazy³⁵ in a patient with slight icterus in the course of exophthalmic goiter. In a second case the anatomical diagnosis was an atrophic, cyanotic nutmeg liver. Microscopical findings for these two were not given. In a third case the liver was described as an atrophic, cyanotic nutmeg liver with an area of coarse lobulation and fatty change, but in the microscopical description only a central cirrhosis was mentioned.

Although our own observations were made in the course of routine autopsies, and without reference to any previous description, search of the literature reveals several references to precisely the same type of interlobular hepatitis as that to be described, in association with exophthalmic goiter. I quote (in translation) from Dinkler's³⁶ description of the liver in his first case: "The liver showed a considerable accumulation of fat droplets in the peripheral cells of certain acini, in the cells of the central regions only by means of the method of Marchi was it possible to demonstrate a deposit of very finely divided fat. In individual areas there were found in the septa of Glisson's capsule submiliary cell-collections, of which the unit elements were in part round and in part oval cells, separated one from another by a fibrillar intercellular substance."

Marine and Lenhart³⁷ wrote: "In a significant number of the long-standing cases [of exophthalmic goiter] coming to autopsy, cirrhosis of the liver has been observed. In the gross such livers are reduced in volume, sometimes smooth, sometimes slightly granular and again distinctly hobnailed. The extent of the connective tissue increase varies from a slight thickening of the portal spaces to well-marked fibrous bands. The liver-cells usually exhibit some degree of fatty metamorphosis." In four of six cases coming to autopsy at Lakeside Hospital, a diagnosis of atrophic cirrhosis was made.

Landau³⁸ found in some cases cirrhotic livers which had not been diagnosed during life. Histologically, this lesion was easily differentiated from stasis-induration. Thus he felt that it must be referred to a toxic etiology.

Although particularly concerned with alterations in the islands of Langerhans, Pettavel³⁹ gave a very good description of changes in the liver

in certain of his cases of exophthalmic goiter. Of the liver of his third case he stated that the connective tissue of the extensions of Glisson's capsule was increased in a patchy manner between the acini. In the increased connective tissue there was a slight lymphocytic infiltration. Rarely the spreading growth of the connective tissue became confluent so that small islands of liver tissue were entirely enclosed by it. New-formed bile ducts were not seen. In the fourth case, also, he referred to the localized interstitial hepatitis, but this case was complicated by miliary tuberculosis. Also Rautmann⁴⁰ described a local increase in the periportal connective tissue, with lymphocytic infiltrations. Such changes he attributed in part to long sustained stasis-hyperemia and in part to preexisting complications (cirrhosis). Yet he recognized a double etiology—circulatory and toxic—for the lipoidosis of the liver cells. The cirrhotic changes in the liver are mentioned also by Holst,⁴¹ who referred to the frequency of urobilinuria in patients with exophthalmic goiter.

Assmann,⁴² whom Lichtman² followed closely, postulated four groups of patients who might show icterus in coincidence with exophthalmic goiter. In the second group he placed those depending upon cardiac insufficiency. Yet he illustrated this group by a case in which the liver showed, in addition to high grade lipoidosis, localized atrophy of the lobules. At the periphery of the atrophic lobules there were increased interstitial connective tissue, infiltration with round cells and slight bile duct proliferation. These changes are not those resulting from chronic passive congestion or stasis. In a third group Assmann placed those cases, chiefly with severe general toxicosis and rapidly lethal outcome, which in the more severe form pass over into an acute yellow atrophy. These he believed to be very probably related etiologically to the hyperthyroidism. The two patients used to illustrate this group both survived so that examination of liver tissue was not possible.

The first clinical observation of a condition which might properly be considered acute yellow atrophy in association with exophthalmic goiter was that of Kerr^{11, 13}. His patient was a male, age 39, who first showed icterus on the fourteenth day following a bilateral partial thyroid lobectomy for hyperthyroidism. Liver dullness was diminished and bile was present in the urine. Death occurred two days later. At autopsy a diagnosis of "hyperplastic goiter with chronic interstitial strumitis" was established. The liver weighed 1290 gm. Its surface was coarsely granular and of light brownish red color. On section, the normal structure was obscured and the color was an opaque reddish-brown with numerous scattered hemorrhagic blotches. On microscopical examination there was almost complete loss of the normal architecture. In the periportal regions there was a marked diffuse infiltration with lymphocytes and some plasma cells. Beyond [central to] these lymphocytic masses were areas showing the remains of necrotic liver cells, infiltrating lymphocytes and leukocytes and hemorrhage. The illustrations accompanying the description show a very extensive necrosis of the parenchyma and fully justify the clinical diagnosis.

In the year following the first report by Kerr, Raab and Terplan¹² described a similar instance under the title of "Basedow's Disease with Subacute Yellow Atrophy" Loss of weight, weakness, vomiting, rapid and sometimes irregular pulse, and icterus had marked the clinical course The liver weighed 1160 gm Consistency was reduced, the cut surface was diffusely yellow with dark red areas, and the periportal and interacinar connective tissue stood out in relief Microscopical examination showed extensive necrosis, lipoidosis, deposits of bile pigment, and localized infiltrations of round cells and leukocytes in the necrotic areas Fibroblastic proliferation and new-formed bile ducts gave evidence of attempted repair The entire picture was that which may properly be called subacute acute-yellow-atrophy of the liver

Barker,⁴⁴ also, has described atrophy and necrosis of the liver in connection with a severe thyro-intoxication

V THE HEPATIC LESIONS IN A SELECTED SERIES OF AUTOPSIES UPON PATIENTS WITH EXOPHTHALMIC GOITER

In the course of routine histological examination of autopsy material from patients who have shown the clinical and histopathological evidence of exophthalmic goiter, such retrogressive changes in the liver as simple and pigment atrophy, cloudy swelling, and particularly degenerative fatty infiltration are noted frequently It is impossible to attach specific significance to such changes because of their very frequent occurrence in a large number of conditions other than thyrotoxicosis Many patients with Graves' disease have been operated upon recently and anesthesia alone may cause degenerative fatty infiltration of the liver While a thyrogenic origin for such acute degenerative processes is not at all unlikely, there is at present no method available for proving that such is the case These changes are probably expressive of rather temporary states in the constantly varying and probably often abnormal metabolism of the liver cells

To a lesion of another type which has been noted from time to time, and to which reference has already been made in the survey of the literature, no such transient character can be attributed This lesion can best be designated as a *patchy chronic parenchymatous interlobular hepatitis* In its slightest form this is made known by a slight enlargement of the islands of Glisson (portal canals) with lymphocyte infiltration In more marked degrees there is a notable increase in the connective tissue, which enlarges the islands so that the liver lobules tend to be encircled by this increased fibrous connective tissue and isolated one from another as in atrophic cirrhosis From the usual form of atrophic cirrhosis, this lesion differs in being irregularly distributed through the substance of the liver, many islands escaping entirely Also, when present to a marked degree, there is a slight intralobular invasion at the periphery of the lobules As compared to atrophic cirrhosis these lesions show less bile duct proliferation in the increased stroma, although some new formation of bile ducts is always present

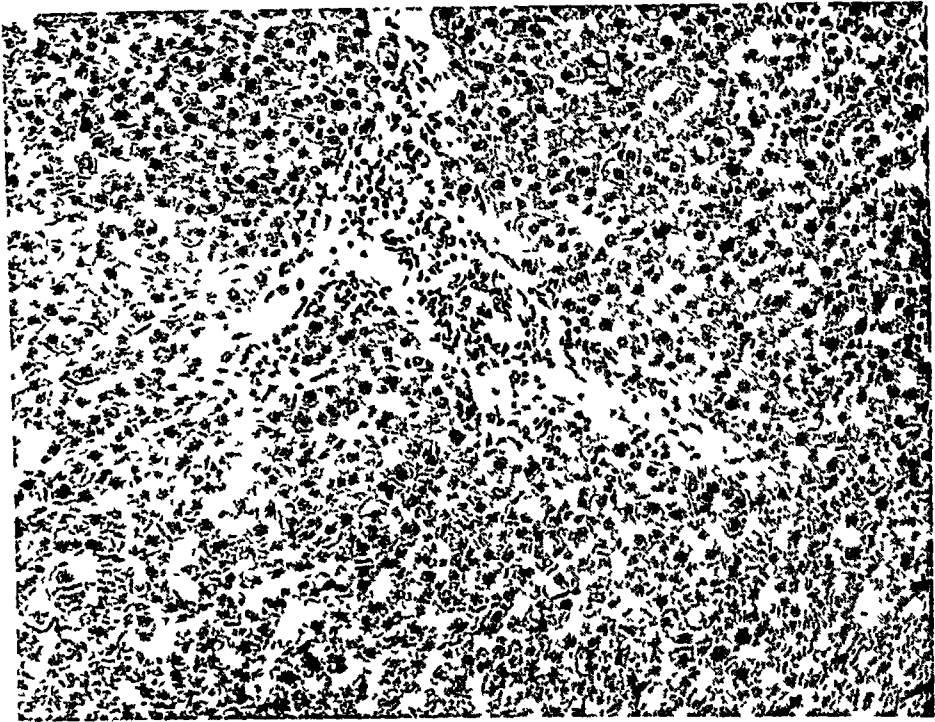


FIG 1 Interlobular hepatitis of slight degree Slight fibrosis and lymphocytic infiltration This and the following photographs are from the livers of patients with exophthalmic goiter

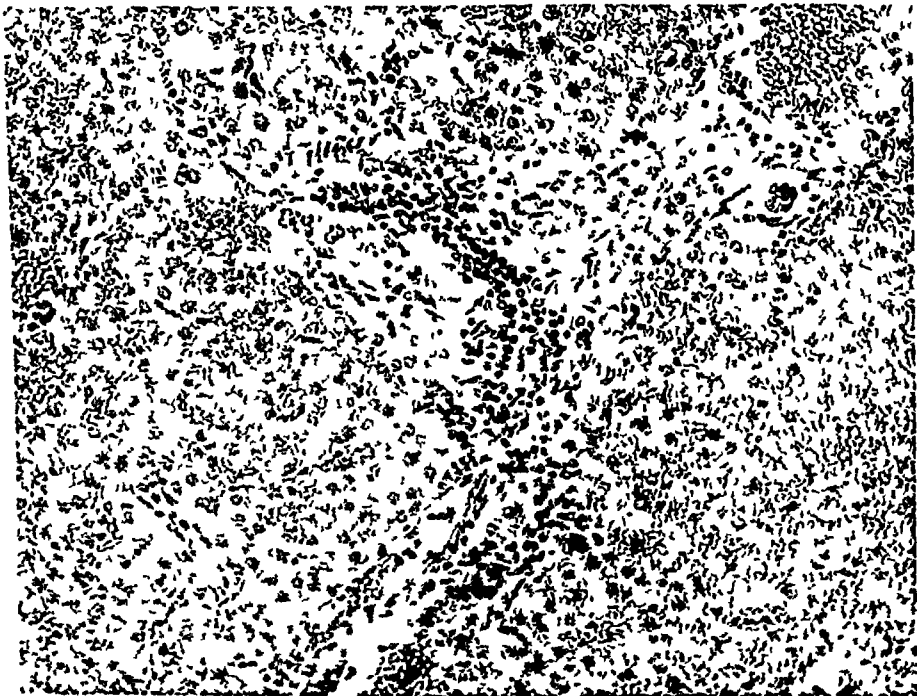


FIG 2 Slightly more marked degree of chronic hepatitis than in the preceding figure Slight bile duct proliferation as well as fibrosis and lymphocytic infiltration in an island of Glisson.

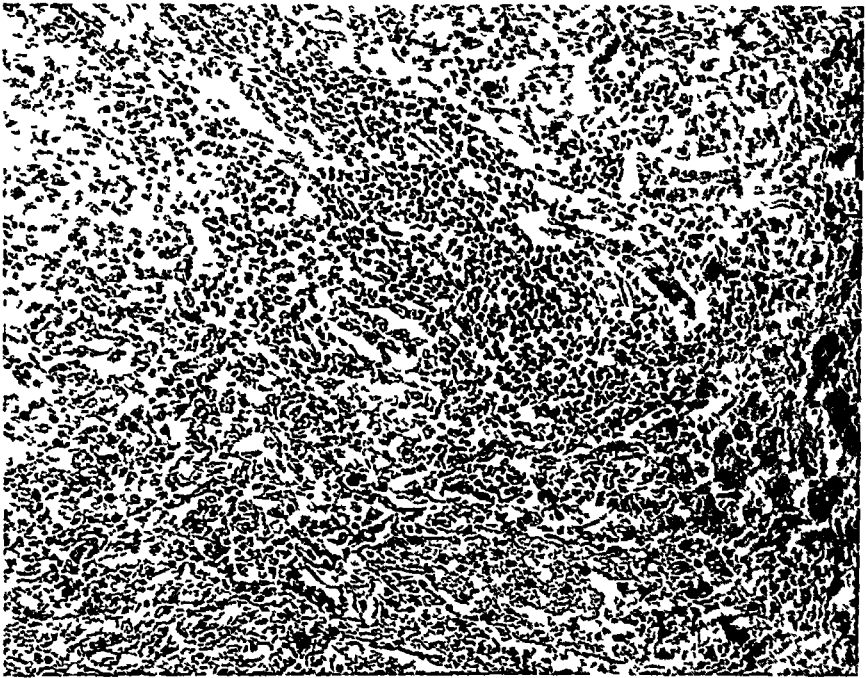


FIG 3 Well marked and active chronic interlobular hepatitis Heavy lymphocytic infiltration Inflammatory process encroaches upon the peripheral zone of the lobules

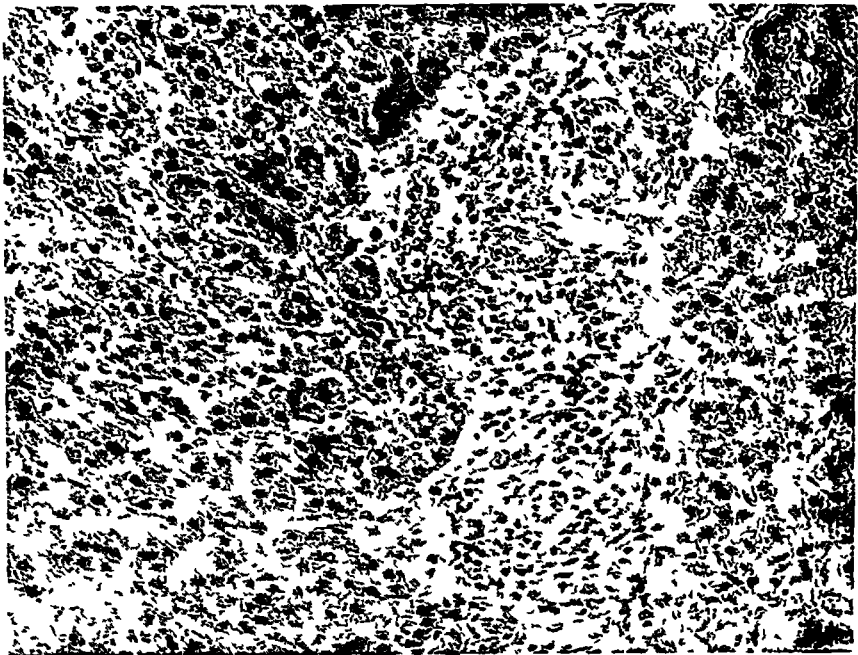


FIG 4 Fibroblastic proliferation and moderate lymphocytic infiltration of the portal canal A less active and presumably older process than that shown in figure 3

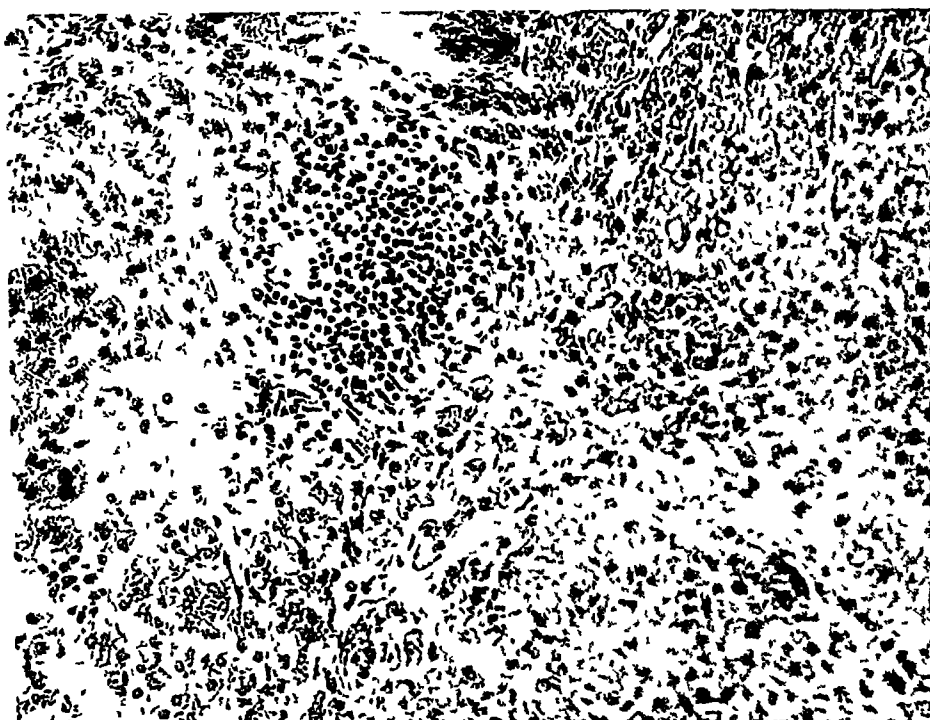


FIG 5 Extensive development of stroma in an island of Glisson. Marked infiltration with lymphocytes. Degenerative fatty infiltration of the neighboring liver cells.



FIG 6 Older residual fibrosis greatly enlarging the island of Glisson. Increased bile ducts.

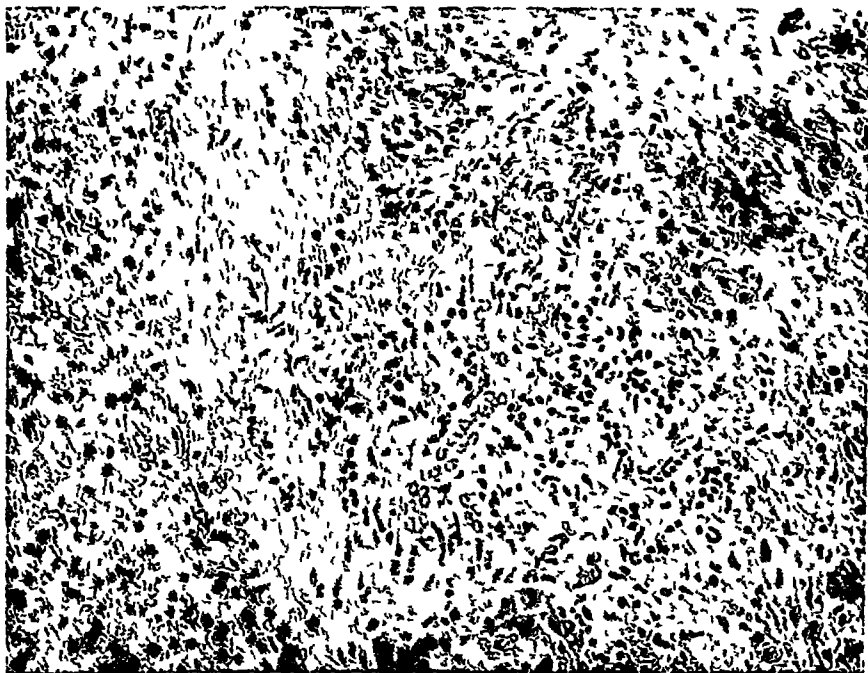


FIG 7 Marked chronic parenchymatous hepatitis from a patient with Graves' disease
Widespread fibrosis, slight bile duct proliferation and diffuse lymphocyte infiltration



FIG 8 Old residual fibrosis in an island of Glisson This shows well the concentric fibrosis frequently seen about the blood vessels of the portal canals

when the islands are greatly increased in size. In an older but not necessarily more extensive stage, the connective tissue may be moderately hyaline in the greatly increased portal canal, and the lymphocytic infiltration reduced to a minimum. Rarely are livers seen with areas of necrosis still present in the parenchyma, but the extensive patchy fibrosis encountered more frequently, having small groups of liver cells scattered through it as in advanced atrophic cirrhosis, may well represent a region in which necrosis has been present. Variations in the extent and age of this form of interlobular hepatitis are shown in figures 1 to 8, all of which are taken from cases used in the series under consideration.

From the microscopical description and the illustrations it will be apparent that this lesion cannot be recognized by the methods of gross pathology when present in the lesser degrees. When more marked the appearances are those of a more or less localized atrophic cirrhosis, a diagnosis which has rather frequently been assigned to such livers as already pointed out in the preceding section of this paper.

Having observed this form of chronic parenchymatous hepatitis in association with exophthalmic goiter in a number of instances, it appeared that there might be a significant correlation between the two conditions. However, impressions thus gained are apt to be deceptive, for when interest is once aroused, the occurrence of the anticipated phenomenon usually carries more weight in memory than its absence. It therefore became desirable to undertake, as far as was possible, a controlled study of the coincidence of such liver changes with exophthalmic goiter. The method of parallel series seemed the only suitable approach.

From a series of 61 autopsies upon patients who had had undoubted clinical manifestations of exophthalmic goiter with the diagnosis verified by microscopical examination, or whose thyroids gave definite histological evidences of that disease even though the clinical diagnosis had not been fully established before death, all were eliminated in which factors known to be significant in the production of hepatitis were present. Thus one or more cases were eliminated for each of the following: latent syphilis, acute and chronic cholecystitis, cholelithiasis, leukemic infiltrations and toxemia of pregnancy. This left a final group of 48, in respect to each of which no known cause of hepatitis existed other than the possibility that it might be due to thyrotoxicosis.

Since chronic hepatitis, particularly in a minimal degree, is occasionally encountered without known cause in the livers of patients who have not had Graves' disease, it became necessary to establish a further control of the selected material. This was done by matching each patient with another of the same sex and of approximately the same age, excluding the same group of conditions known to produce pathological changes in the liver, but also excluding Graves' disease. The incidence of chronic hepatitis was then ascertained in the two series with the following result:

	Graves' disease	Control series
No chronic hepatitis	6	33
Slight chronic hepatitis	16	14
Well-marked chronic hepatitis	26	1
	<hr/> 48	<hr/> 48

Care was taken to use the same standards throughout. Chronic hepatitis of slight degree occurred with approximately the same frequency in both series. Under this heading were placed all livers showing a slight increase in size of the portal canals with small infiltrations of lymphocytes. It is doubtful whether a reaction of this degree can be considered of significance in the present investigation. In the Graves' disease series but six were without hepatitis, while this was true of 33 of the control series. On the other hand 26 of the Graves' disease series showed a well-marked chronic hepatitis as compared to one in the control series. (This single case may have some special interest. Review of the protocol showed that this patient, whose death was caused by a pituitary tumor, had a well-marked hypoplasia of the adrenals. Since adrenal hypoplasia is of constant occurrence in individuals with the Graves' constitution, there may be a significant relationship involved.)

Such a marked difference in the occurrence of hepatitis in the two series seems to establish the fact that a definite significance attaches to the coincidence of Graves' disease and chronic interlobular hepatitis of the type described. Whether a direct or indirect causal relationship exists between them cannot be answered with certainty at the present time. It is not unreasonable to surmise that the same active principle, which in small amounts increases the metabolic activity of the liver and leads even to hypertrophy of the organ, and in somewhat larger amounts causes the discharge of stored glycogen and inhibits glycogenic function, may in still larger amounts prove actively destructive, producing localized degenerative changes and even necrosis. Furthermore, it is easy to reconcile the cirrhotic effect of such an agent acting in a moderate degree for a prolonged period with the actively necrosing effect observed in those examples of exophthalmic goiter in which the clinician, properly enough, has made a diagnosis of acute yellow atrophy of the liver. Thus it seems probable that the patchy interlobular hepatitis found associated with Graves' disease, like the more or less similar forms of chronic hepatitis of which the etiology is known, is directly or indirectly of toxic origin. The suggestion that this hepatitis is of circulatory origin can be dismissed by calling attention to its peripheral position in the lobule. Chronic passive congestion, "nutmeg liver," asphyxiative central necrosis, or even a so-called central cirrhosis may be present without in any way resembling or creating confusion with the island changes and peripherally encroaching hepatitis found in so many of the patients with Graves' disease.

It is not within the scope of this paper to undertake an analysis of the

very difficult question as to whether there is a correlation between the extent and severity of the liver changes and the general intensity of thyrotoxicosis as gauged by clinical standards. There is some evidence to show that such a correlation exists, particularly in those cases in which there are evidences of extensive damage to the liver parenchyma.

SUMMARY

That the liver may be, and frequently is, involved in Graves' disease is shown *clinically* by the occasional occurrence of icterus, marked degrees of which are known to be of serious import in this disease, *physiologically*, by the accumulating evidence of altered liver function in such patients, *experimentally*, by the evidence of hepatic dysfunction following administration of thyroid substance and thyroxin, and *morphologically*, by structural changes in the liver, varying from slight degrees of chronic hepatitis to a widespread degenerative and necrotizing process which must be considered an "acute yellow atrophy." In a series of 48 carefully selected cases of Graves' disease, well-marked hepatitis was found in 54 per cent, while a matched control series of the same size yielded but a single case (2 per cent) with well-marked hepatitis. As usually seen, this liver lesion is interlobular, is patchily distributed, involves the peripheral portion of the lobules to a moderate degree, and shows relatively more fibrosis and lymphocyte infiltration than bile duct proliferation. It may be characterized as a *patchy chronic parenchymatous interlobular hepatitis*. Correlation with the severity and duration of thyrotoxicosis is indicated, but as yet unproved.

REFERENCES

- 1 WELLER, C. V. Hepatic lesions associated with exophthalmic goiter, *Trans Assoc Am Phys*, 1930, xlv, 71-75.
- 2 LICHTMAN, S. S. Liver function in hyperthyroidism, *Arch Int Med*, 1932, 1, 721-729.
- 3 HARRISON, S. O. Exophthalmic goiter, heart disease, jaundice, death, *Lancet*, 1874, i, 510.
- 4 EGER. Beitrag zur Pathologie des Morbus Basedowii, *Deutsch med Wchnschr*, 1880, vi, 153-157.
- 5 SUTCLIFF, E. H. An extraordinarily acute case of Graves' disease, *Lancet*, 1898, i, 717.
- 6 EDER, M. D. Three cases of jaundice occurring in persons suffering from exophthalmic goiter, *Lancet*, 1906, i, 1758.
- 7 SATTLER, H. Die Basedowsche Krankheit, in Graefe-Saemisch, *Handbuch der gesamten Augenheilkunde*, 1908, Engelmann, Leipzig, Vol ix, pt 2.
- 8 BOOTHBY, W. M. Diagnosis and treatment of the diseases of the thyroid gland, 1922, *Oxford Medicine*, Oxford Univ Press, New York City, Vol iii, pp 917, 925.
- 9 CROFT, A. Thyroid and thymus, 1922, second edition, Lea and Febiger, Philadelphia and New York.
- 10 HILMEYER, L. Blutarbeitsstoffwechselstudien. 3. Mitteilung Blutmauserung und Leberfunktion beim Morbus Basedow, *Deutsch. Arch f klin Med*, 1931, cxix, 515-528.
- 11 KERR, W. J., and RUSK, G. Y. Acute yellow atrophy associated with hyperthyroidism, *Med Clin N Am*, 1922, vi, 445-459.
- 12 RAB, W., and TERILAN, C. Morbus Basedowii mit subakuter Leberatrophie, *Med Klin*, 1923, xix, 1154-1156.

- 13 HIROSE, M Über die alimentare Galaktosurie bei Leberkrankheiten und Neurosen, Deutsch med Wchnschr, 1912, **xxviii**, 1414-1416
- 14 STRAUSS, H Über neurogene und thyreogene Galaktosurie, Neurol Centralbl, 1913, **xxviii**, 1281-1284
- 15 SANGER, B J, and HUN, E G Glucose mobilization rate in hyperthyroidism, Arch Int Med, 1922, **xxv**, 397-406
- 16 YOUMANS, J B, and WARFIELD, L M Liver injury in thyrotoxicosis as evidenced by decreased functional efficiency, Arch Int Med, 1926, **xxxvii**, 1-17
- 17 PENDE, N Leber und Schildrüse Die Hyperfunktion der Leber bei Basedowkranken, Endokrinologie, 1928, **i**, 161-167
- 18 KUGELMANN, B Über Störungen im Kohlehydratstoffwechsel beim Morbus Basedow, Klin Wchnschr, 1930, **ix**, 1533-1534
- 19 DRESEL, K., and GOLDNER, M Ein neuer biologischer Test für Schilddrüsenstoffe, Verhandl d deutsch Gesellsch f inn Med, 1929, **xli**, 534
- 20 WILLIS, D A, and MORA, J M Biological reaction for hyperthyroidism, Proc Soc Exper Biol and Med, 1931, **xxviii**, 562-563
- 21 HIMMELBERGER, L R Thyroid hormone in blood and urine in Graves' disease, preliminary paper, Endocrinology, 1932, **xi**, 264-266
- 22 SCHRYVER, S B Researches on the autolytic degradation of tissues Part II On the influence of the thyroid on autolysis, Jr Physiol, 1905, **xxxii**, 159-170
- 23 CRAMER, W, and KRAUSE, R A Carbohydrate metabolism in its relation to the thyroid gland, the effect of thyroid feeding on the glycogen content of the liver and on the nitrogen distribution in the urine, Proc Roy Soc London, Series B, 1913, **lxxxvi**, 550-560
- 24 PARHON, M Sur la teneur en glycogène du foie et des muscles chez les animaux traités par des préparations thyroïdiennes, Jr de physiol et de path gén, 1913, **xv**, 75-78
- 25 KURIYAMA, S The influence of thyroid feeding upon carbohydrate metabolism, Am Jr Physiol, 1917, **xliii**, 481-496 The influence of thyroid feeding upon carbohydrate metabolism I The storage and mobilization of the liver glycogen in thyroid-fed animals, Jr Biol Chem, 1918, **xxviii**, 193-205
- 26 FUKUI, T Über den Kohlenhydratverlust der Leber hyperthyreoidisierter Ratten Zugleich ein Beitrag zur Frage der Wertbestimmung von Schilddrüsenpräparaten, Arch f d ges Physiol, 1925, **ccv**, 410-426
- 27 REINWEIN, H., and SINGER, W Studien über Gewebsatmung IV Mitteilung Der Einfluss von Thyroxin, Adrenalin und Insulin auf den Sauerstoffverbrauch überlebender Leberzellen, Biochem Ztschr, 1928, **cxcvii**, 152-159
- 28 DRESEL, K., GOLDNER, M., and HIMMELWEIT, F Zum Basedowproblem, Deutsch med Wchnschr, 1929, **lv**, 259-261
- 29 SIMONDS, J P, and BRANDES, W W Effect of experimental hyperthyroidism and of inanition on the heart, liver and kidneys, Arch Path, 1930, **ix**, 445-460
- 30 HEFWITT, J A The effect of administration of small amounts of thyroid gland on the size and weight of certain organs in the male white rat, Quart Jr Exper Physiol, 1919-20, **xii**, 347-354
- 31 HOSKINS, E R The growth of the body and organs of the albino rat as affected by feeding various ductless glands (thyroid, thymus, hypophysis, and pineal), Jr Exper Zool, 1916, **xxi**, 295-346
- 32 FARRANT, R Hyperthyroidism its experimental production in animals, Brit Med Jr, 1913, **ii**, 1363-1367
- 33 HASHIMOTO, H Heart in experimental hyperthyroidism with special reference to its histology, Endocrinology, 1921, **v**, 579-606
- 34 FARNER, E Beiträge zur pathologischen Anatomie des Morbus Basedowii mit besonderer Berücksichtigung der Struma, Arch f path Anat, 1896, **cxliii**, 509-574

- 35 ASKANAZY, M Pathologisch-anatomische Beiträge zur Kenntnis des Morbus Basedowii, insbesondere über die dabei auftretende Muskelerkrankung, Deutsch Arch f klin Med, 1898, lxi, 118-186
- 36 DINKLER Über den klinischen Verlauf und die pathologisch-anatomischen Veränderungen eines schweren durch Hemiplegie, bulbare und psychische Störungen ausgezeichneten Falles von Basedowscher Krankheit, Arch f Psych u Nervenheilk, 1900, xxxiii, 335-365
- 37 MARINE, D, and LENHART, C H Pathological anatomy of exophthalmic goiter, the anatomical and physiological relations of the thyroid gland to the disease, the treatment, Arch Int Med, 1911, viii, 265-316
- 38 LANDAU Die pathologische Histologie der Basedowstruma, München med Wchnschr, 1911, lviii, 1213
- 39 PETTAVEL, C A Beitrag zur pathologischen Anatomie des Morbus Basedow, Deutsch Ztschr f Chir, 1912, cxvi, 488-543
- 40 RAUTMANN, H Pathologisch-anatomische Untersuchungen über die Basedowsche Krankheit, Mitt a d Grenzgeb d Med u Chir, 1915, xxviii, 489-618
- 41 HOLST, J Untersuchungen über die Pathogenese des Morbus Basedowii (der Thyreosen), 1923, Supp IV, Acta Chir Scand, P A Norstedt and Sons, Stockholm and Kristiania, 212 pp
- 42 ASSMANN, H Leber und Milz bei Morbus Basedow, München med Wchnschr, 1931, lxxviii, 221-225
- 43 KERR, W J Necrosis of heart and liver in thyrotoxicosis, with some notes on possible changes in other organs, Northwest Med, 1930, xlix, 430-431
- 44 BARKER, L F Thyreo-intoxication with necrosis and atrophy of liver, damage to heart muscle and kidneys, and terminal bronchopneumonia, Med Clin N Am, 1930, xiv, 261-263

A PAINLESS HISTAMINE SKIN TEST: AN EXPERIMENTAL STUDY *

By SAMUEL PERLOW, M D , *Chicago, Illinois*

IN 1927 Thomas Lewis¹ demonstrated that the histamine skin reaction consisted of three distinct factors, (1) a local dilatation of the capillaries, venules, and arterioles by direct action which caused a purplish areola, (2) a local increase in the permeability of the walls of the minute vessels by direct action, which caused a wheal at the site of the injection, and (3) a widespread dilatation of the surrounding arterioles by local reflex action, which was visible as a red flare. He also demonstrated that if the circulation was cut off completely a purple spot would appear but no wheal or flare, and that coldness of the skin retarded the reaction. In 1928 Starr² used this test in a study of peripheral circulation in diabetics. Using the method of pricking the skin through a drop of histamine, he found that the changes suggesting a reduction in circulation were (1) delay in the appearance of the reaction, (2) delay in the appearance plus a reduction of the intensity of the reaction, (3) failure of either flare or wheal to appear, (4) failure of both the flare and the wheal to appear and the reaction to consist of only a purple spot which was a sign of complete obstruction of arterial circulation. With this method of performing the test, Starr found that normally the reaction was at its height in two and one-half to five minutes.

De Takats³ modified the method of performing the test, and instead of puncturing the skin through a drop of histamine he injected 0.1 c.c. of 1:1000 histamine solution intradermally. The reactions by this method are the same as those described by Starr. The areola is a narrow purplish border about the site of the injection. The wheal is irregular but sharply defined and is usually one-half to one centimeter in diameter. The flare surrounding it is also irregular but is not raised and extends for one to two centimeters in each direction. In the Peripheral Circulatory Clinic of the Michael Reese Hospital our experience has been that the reaction is more intense and easier to read when the histamine is injected intradermally than when the skin is pricked through a drop of the solution. The test is fairly accurate as a means of determining circulatory efficiency and agrees closely with the oscillometric readings and the skin temperatures. Besides diminution in circulation other factors which cause a delayed or absent reaction are degeneration of cutaneous nerves, previous use of histamine in the same spot, injury of the skin by ultra-violet and roentgen-ray or burns, and various skin diseases.

One of the great faults of the test when performed by the method of intradermal injection is its painfulness. Although the pain lasts only a

* Received for publication April 15, 1933

From the Peripheral Circulatory Clinic of the Michael Reese Hospital

TABLE I

Because 1 1000 histamine solution was the standard used in the Peripheral Circulatory Clinic, its reactions were graded + + + + + in this series of tests A + + + + + areola is one 1/2 to 1 mm wide about the primary wheal made by the injection A + + + + + wheal is the irregular secondary wheal 4 to 5 mm in diameter A + + + + + flare is one 2 cm to 3 cm in diameter and of intense pink color

Solution	Pain	Areola	Wheal	Flare	
				5 Min	10 Min
1 10000 Histamine	+ for 2"	+ + + + + in 10"	+ + + + + in 3'	+ +	+ +
1 2000 "	+ " 2"	+ + + + + " 10"	+ + + + + " 3'	+ +	+ +
1 1000 "	+ " 2"	+ + + + + " 10"	+ + + + + " 3'	+ +	+ +
2 1000 "	+ + + + + " 20"	+ + + + + " 10"	+ + + + + " 3'	+ +	+ +
4 1000 "	+ + + + + " 20"	+ + + + + " 5"	+ + + + + " 1'	+ +	+ +
1% Novocaine	0	+ + + + + " 10"	0	0	0
1% "	0	+ + + + + " 10"	0	0	0
2% "	0	+ + + + + " 10"	0	0	0
4% "	0	+ + + + + " 10"	0	0	0
1 2000 Histamine in 1% Novocaine	0	+ + + + + " 10"	+ + + + + in 3'	+ +	+ +
1 2000 "	+ for 1"	+ + + + + " 10"	+ + + + + " 3'	+ +	+ +
1 1000 "	0	+ + + + + " 10"	+ + + + + " 3'	+ +	+ +
1 1000 "	0	+ + + + + " 10"	+ + + + + " 3'	+ +	+ +
1 1000 "	0	+ + + + + " 10"	+ + + + + " 3'	+ +	+ +
2 1000 "	0	+ + + + + " 10"	+ + + + + " 3'	+ +	+ +
2 1000 "	+ + for 20"	+ + + + + " 5"	+ + + + + " 1'	+ +	+ +
2 1000 "	+ " 20"	+ + + + + " 5"	+ + + + + " 1'	+ +	+ +
2 1000 "	0	+ + + + + " 5"	+ + + + + " 1'	+ +	+ +
2 1000 "	0	+ + + + + " 60"	+ + + + + " 10'	0	+
Needle prick through 1 1000 histamine					

second or two, its excruciating sharpness frequently gives rise to bitter complaints on the part of the patient, especially when it is necessary to repeat the tests at intervals to note changes in peripheral circulation. The work here reported was undertaken with a view to establishing some modification of the test which would be as rapid and as accurate as the 1:1000 histamine intradermally but not as painful. Various dilutions of histamine alone and in combination with novocaine were tried. In table 1 is a list of solutions used and of the results obtained. The tests were performed on the volar surface of the forearm of a normal subject. In each case sufficient solution was injected intradermally to make a primary wheal 2 mm. in diameter and the pain due to the insertion of the needle was discounted.

A study of the table reveals that the size of the reaction and the intensity of the pain vary directly as the concentration of the histamine when used alone. To prevent the pain, correspondingly stronger solutions of novocaine are necessary. The combinations which gave excellent histamine reactions without pain were 1:2000 histamine in $\frac{1}{2}$ per cent, 1 per cent and 2 per cent novocaine, 1:1000 histamine in 1 per cent and 2 per cent novocaine and 2:1000 histamine in 2 per cent novocaine. Although the stronger solutions of histamine gave more rapid and more intense reactions the severe inflammatory changes that they induce constitute a serious objection. When 2:1000 histamine and 4:1000 histamine solutions were used, alone or with novocaine, a hemorrhagic inflammatory area was formed at the site of the injection which persisted for several days. As these severe reactions were obtained in normal skin, one can readily see the danger of using such strong solutions of histamine in testing skin with deficient circulation. In such cases it is best to use the weakest solutions which give good reactions.

We have found that 1:2000 histamine in $\frac{1}{2}$ per cent novocaine is such a solution. The test is painless and the reaction in the skin is intense and rapid enough to be practical. To determine the efficiency of this solution in skin with deficient circulation a few such cases were tested. (Table 2.) There was no noticeable difference between the reactions following injections of 1:1000 histamine and those produced by 1:2000 histamine in $\frac{1}{2}$ per cent novocaine.

The results of this series of tests showed that skin with deficient circulation reacted as intensely to 1:2000 histamine in $\frac{1}{2}$ per cent novocaine solution as it did to 1:1000 histamine alone. In both cases the height of the reaction was reached in 10 minutes.

CONCLUSION

A painless but efficient histamine skin reaction may be obtained by injecting intradermally 1:2000 histamine in $\frac{1}{2}$ per cent novocaine solution. The reaction may be read at five minutes but is best read at 10 minutes when it is at its height.

The author wishes to thank Dr Ralph B Bettman and Dr Samuel Soskin for suggesting this research

BIBLIOGRAPHY

- 1 LEWIS, T The blood vessels of the human skin and their responses, 1927, Shaw and Sons, Ltd, London
LEWIS, T, and GRANT, R T Vascular reactions of skin to injury, liberation of a histamine-like substance in injured skin, the underlying cause of factitious urticaria and of wheals produced by burning, and observations upon nervous control of certain skin reactions, Heart, 1924, xi, 209-265
- 2 STARR, I, JR Change in reaction of skin to histamine as evidence of deficient circulation in lower extremities, Jr Am Med Assoc, 1928, xc, 2092-2094
- 3 DE TAKATS, G Cutaneous histamine reaction as test for collateral circulation in extremities, Arch Int Med, 1931, xlviii, 769-785

INTRAVENOUS VACCINE THERAPY IN CHRONIC ARTHRITIS * †

By WILLIAM B RAWLS, M D , F A C P , B J GRUSKIN, M D , and
A RESSA, M D , *New York, N. Y*

MUCH attention has been focused on the subject of chronic arthritis during the past few years and a survey of the literature shows an increasing belief in the streptococcal etiology of this condition ^{1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11}

Many points of similarity have been noted between chronic arthritis, especially the so-called rheumatoid type, and rheumatic fever ¹² Menzer, ¹³ in 1902, in an endeavor to explain the peculiar action of his serum in rheumatic fever, advanced a theory which, in many respects, resembles the modern concept of allergy More recently, Swift ^{14, 15, 16, 17} and Zinsser ^{18, 19} have brought forth evidence that the pathogenesis of rheumatic fever can be explained by the existence in certain individuals of a condition of hypersensitiveness (allergy or hyperergy) to streptococci, resulting from repeated low grade infection or from the persistence of foci of infection in the body This hypothesis has been applied in a measure also to chronic arthritis Cecil ⁷ believed that bacterial allergy might or might not influence the clinical picture of chronic arthritis

Experimental investigations by Swift et al ^{20, 21, 22, 23} on the reactions of animals to infection with streptococci under various conditions, have shown that the reactive state of these animals was conditioned largely by the mode of inoculation When made directly into the tissues, the resulting state was that of hyperergy but when the preliminary inoculation had been made intravenously, the resulting state was one of immune hyposensitivity It has been shown ^{15, 21} that hypersensitive animals can be rendered immunely hyposensitive by suitable intravenous vaccination

Assuming that hyperergy played a rôle in chronic arthritis and reasoning that the hypersensitive state might be influenced, as shown by Swift in animal experimentation, we were prompted early in 1930 to study the effects of the intravenous use of phenolized, unheated, autogenous vaccines prepared from organisms with high agglutinin titers The necessity of

* Presented as a Clinic at the Montreal Meeting of the American College of Physicians, February 8, 1933

From the Arthritis Clinic of the New York Polyclinic Medical School and Hospital

† While this paper was in preparation the following articles appeared

- 1 CLAWSON, B J, and FAHR, G E Experiments leading to a possible basis for vaccine therapy in acute rheumatic fever, *Proc Soc Exper Biol. and Med*, 1930, xxvii, 964-965
- 2 SWIFT, H F, HITCHCOCK, C H, DERICK, C L, and McEWEN, C Intravenous vaccination with streptococci in rheumatic fever, *Am Jr Med Sci*, 1931, clxxvi, 1-11
- 3 WETHERBY, M, and CLAWSON, B J Chronic arthritis, with special reference to intravenous vaccine therapy, *Arch Int Med*, 1932, lxi, 303-320
- 4 CLAWSON, B J, and WETHERBY, M Experimental basis for intravenous vaccine therapy in chronic arthritis with summary of results obtained in patients, *ANN INT MED*, 1932, v, 1447-1461

suitably controlling this work was realized. A group of patients was then selected, many of whom had previously received other types of treatment before coming under our care. No other form of medication was used. A routine clinical study, consisting of the following, was made on each patient:

- 1 Special history and physical examination with emphasis on evidence of existing or past rheumatic affections or other allergic phenomena
- 2 Special examination by the Nose and Throat, Dental, Genito-Urinary, Gastrointestinal and Gynecological Departments
- 3 Urinalysis
- 4 Culture of stool
- 5 Nose and throat cultures (these were repeated in the case of indefinite findings)
- 6 Complement fixation using a number of antigens composed of pooled strains of their respective bacterial groups
- 7 Sedimentation rate
- 8 Agglutination reactions with autogenous organisms using the patient's own blood serum
- 9 Basal metabolism
- 10 Complete blood count

The bacteriologic and serologic studies were made as follows:

Complement fixation reactions, and cultures of the nose, throat and feces were made on all patients. Agglutination reactions were made with all smooth strains isolated. Several reexaminations were necessary in some cases. Cultures of teeth, gall-bladder or other foci were also made where necessary. Those organisms having an agglutinin titer of 1:160 or above were considered pathogenic.

Throat swabs were incubated in Rosenow's brain heart infusion over night. The following morning they were stirred around in the medium and discarded. The cultures were then allowed to stand a few hours to permit settling of the gross particles and the floccules of rough organisms. Blood agar plates were inoculated from the supernatant fluid and incubated in Varney phosphorus jars. Some streptococci having high agglutinin titers grew poorly in aerobic cultures and successful cultures were more readily obtained in the phosphorus jars.

Each type of colony appearing on the blood agar plates was transferred to other blood agar plates in order to obtain pure cultures. Incubation in the anaerobic jars permitted a greater differentiation of the various types of colonies than was possible by the usual methods.

The pure growths were scraped from the blood agar plates and transferred to 50 c.c. bottles of Rosenow's medium. A dense growth was usually obtained over night. The growths were examined the following morning and tested for purity. Rough strains were discarded. The smooth strains were centrifuged and emulsified in 5 c.c. of 0.5 per cent phenol in normal saline. After taking a small amount for the agglutina-

tion reaction, the tubes were stored in the refrigerator for future reference

For the agglutination reaction, a series of tubes containing about 11 c c of saline were placed in a rack. The heavy suspensions were added to these tubes until the density approximated 100 millions per c c. The tubes were allowed to stand for two hours to permit the coarser particles to settle. Serum dilutions were prepared ranging from 1:40 to 1:10,240. A saline control was used. An equal volume of the decanted suspension was added to each of the tubes of diluted serum, and they were vigorously shaken and placed in the water bath at 51° C for two hours. They were then allowed to stand over night at room temperature. Critical comparison was necessary for an accurate determination of the end-point. Those organisms having an agglutinin titer of 1:160 or over were washed a second time and preserved. The others were discarded. Each suspension was tested for sterility before being mixed with the rest of the vaccine.

The injections were given once or twice weekly. At each time the reactions following the previous injection were recorded. (See chart 1.) The same type of syringe and the same gauge needle were used and, in calculating the dose, allowance was made for the capacity of the needle.

In the beginning, patients receiving intravenous injections of vaccine were taught to take their temperature and were requested to do so at two-hour intervals during the afternoon of the day of treatment and the following day.

The reactions following the intravenous injection of vaccines were as a rule focal, rather than general in nature, the latter having been eliminated by adoption of the procedure outlined below. Other workers have used large initial doses which resulted in general reactions with elevation of temperature. This made it difficult to determine the influence of protein shock as a factor in their work, and their dosage, therefore, was not comparable with ours.

Since we were dealing with ambulatory patients who were seen for a short period once or twice weekly, the early treatments had to be instituted with considerable caution. We began by giving initial doses of 5,000 organisms, but this frequently produced a general reaction with chills and elevation of temperature. (See Case I.) In order to avoid a general reaction, it was found necessary to give an initial dose of not more than 500 bacteria. In many instances, however, it was found that this dose would produce a severe focal reaction. One ambulatory patient was confined to bed for four weeks following an even smaller dose. (See Case II.)

The average initial dose was then gradually reduced until a reaction was no longer encountered in the majority of patients. This dose was found to be about 10 to 20 organisms, depending somewhat on the severity of the disease. A few of our patients have not been able to tolerate even this small dose. They showed marked improvement, however, when the dose was further reduced to 4 or 5 organisms. In a small group of cases, a larger dose could undoubtedly have been given without producing either

a focal or general reaction, but the possibility of causing a severe focal reaction was too great to warrant such a procedure (See Case II) In the beginning, the dose was increased as rapidly as possible but not sufficiently to produce an elevation of temperature or a severe focal reaction In a number of instances, however, this rapid increase was followed by premature ventricular contractions, precordial pain, severe fatigue, dizziness, sinus tachycardia, loss of weight, headaches, insomnia, extreme unexplained nervousness, disturbances in vision, diarrhea and severe mental depression sometimes simulating mild encephalitis Regardless of these reactions, some showed improvement in the focal symptoms (See Cases III and IV)

CASE I

Mrs J L, white, female, aged 45, diagnosis, advanced rheumatoid arthritis *Streptococcus viridans* (Brown's classification), having an agglutinin titer of 1 5120, was isolated from the throat and a vaccine made from it An initial dose of 5,000 was given A severe chill occurred five minutes later Two hours later, the temperature reached 103° F There was also a severe delayed focal reaction Five days later, a dose of 1,000 organisms was given which was followed by a slight general reaction manifested by a slight chill and a temperature of 100.5° F The dose was then increased to 1,000, 1,500, 2,000 and 2,500 organisms at five day intervals without any general reaction Five days later, 4,000 organisms were given (an increase of 60 per cent) This was followed by a moderate general reaction with a chill, the temperature reaching 101° F The dose was then repeated without any reaction Five days later the patient received 6,000 organisms (an increase of 50 per cent) which was followed by a general reaction, the temperature again reaching 101° F The next four doses were increased at the rate of 10 per cent with no apparent reactions The percentage of increase was then slowly raised to 25 per cent without producing any general reaction

This case demonstrates the difficulties encountered at the beginning of this work It also illustrates our contention that the percentage of increase by this method should be small

CASE II

M G M, white, male, aged 24, diagnosis, rheumatoid arthritis The patient was well until June 1930, when he complained of vague pain in the left hip and both knees which gradually extended to other joints and became more severe Roentgen-ray examination of the spine in September 1931, revealed ankylosing arthritis (Marie-Strumpell disease) involving the entire spine, also marked arthritis of both hips, wrists, fingers, etc A hemolytic streptococcus with an agglutinin titer of 1 640 was isolated from the throat An initial dose of 300 of these organisms was given, with no general reaction On the other hand, there was a severe focal reaction with marked increase of pain in the right hip, sacro-iliac joints, knees, and entire spine, and the patient was confined to bed The pain was severe and was not relieved by the usual anti-rheumatic drugs The pain continued to be severe for two weeks, after which there was slow improvement He was able to be out of bed four weeks from the date of the inoculation Six weeks after the injection he had not fully recovered and had more difficulty in walking than previous to the injection of the vaccine A dose of 10 organisms at this time did not produce a reaction He then stated that he had previously been given vaccine treatments and usually experienced severe focal reactions With our present knowledge of the necessity of a small initial dose, depending somewhat on the severity of the disease, we would have begun with 15 or 20 organisms

This case illustrates the extreme type of focal reaction which may occur even with a comparatively small dose and this reemphasizes the risk of employing large initial doses.

CASE III

J W, physician, white, male, aged 52, diagnosis, rheumatoid arthritis of five years' duration involving both feet, ankles and both hands. An alpha type streptococcus having an agglutinin titer of 1 1280, was recovered from the throat. An initial dose of 500 organisms was given which was increased about 25 per cent at four day intervals until a total of 12,000 organisms was reached. Following this dose there was dizziness, precordial pain, severe nervousness, tachycardia and insomnia. The precordial pain was occasionally severe and at other times dull and aching in character. The pain, nervousness, tachycardia and insomnia persisted for 48 hours and then disappeared. The dose was then reduced to 5,000 organisms which did not produce an untoward reaction. It was then increased to 7,000 and 8,000 organisms with no unfavorable result. Five days later, a dose of 10,000 organisms was given and this was again followed by precordial pain, palpitation, nervousness, dizziness, insomnia and fatigue. An electrocardiogram was taken at this time, and again after all symptoms of the reaction had disappeared. In the first record premature beats were observed which were no longer present when the second record was taken. The dose was reduced to 3,000 which was followed by a beneficial response. It was then increased 10 per cent each time with no unfavorable reaction, until the dose reached 14,000 organisms when the above symptoms reappeared. Since that time the focal symptoms have been markedly improved.

CASE IV

Mrs S R B, white, female, aged 33, diagnosis, early rheumatoid arthritis involving the fingers of both hands, both wrists, cervical spine and both knees. The symptoms began one year before, appearing immediately after childbirth and steadily increasing. About three months before, the tonsils were removed without apparent improvement. Two infected teeth were extracted from which a smooth strain of *Streptococcus viridans* with an agglutinin titer of 1 640 was obtained and from which a vaccine was made. Cultures of the nose and throat yielded strains of *Streptococcus hemolyticus* with negative agglutinin titers. They were not used in the preparation of a vaccine as they were considered unimportant. Stool cultures were negative. Roentgenograms of the hands, wrists and fingers revealed early arthritis. An initial dose of 50 organisms of the *Streptococcus viridans* strain was given on November 13, 1931. The dose was slowly increased according to chart 1 until December 28, when 500 organisms were given. This was followed by a slight focal reaction, nervousness and marked dizziness. On January 4, the dose was increased to 700 organisms resulting in nervousness, insomnia, inability to concentrate and loss of appetite. The dose was repeated January 8 and 13. The effects were similar to those caused by the previous injection. On January 18, the patient still complained of dizziness, occasional attacks of double vision with inability to read, was very irritable, depressed and cried frequently. She also complained of palpitation and an occasional precordial pain. The vaccine was discontinued until January 28. By this time the nervousness had diminished, the dizziness had entirely disappeared, there was considerably less fatigue, less insomnia and her appetite was improved. A dose of 50 bacteria was then given which was slowly increased every four days until March 23, when it had reached 400 bacteria. This was followed by dizziness, nervousness, fatigue and insomnia. Lowering the dose was accompanied by disappearance of these symptoms. Since the patient was not receiving other medication, and once these symptoms disappeared after the dose had been reduced, it is reasonable to attribute the ill effects to the vaccine. The focal symptoms were improved in spite of the constitutional reactions.

The above cases are presented to illustrate the toxic reactions which sometimes followed the use of comparatively small doses of vaccine

In order to avoid such reactions, it was found necessary to reduce the percentage increase of the vaccines until these symptoms were no longer encountered. It was considered advisable to establish a procedure which would have a tendency to eliminate the above difficulties. Criteria for determining and tabulating reactions were then established. These were used as a basis for the following outline of vaccine dosage which has been adopted as a standard procedure (chart 1)

CHART I
Criteria for Determining Reactions and Suggestions for Dosage

Type of Reaction	Symptoms and Signs	Suggestion for Dosage Intravenous Method
1 Focal	Increased pain, tenderness, redness, swelling and/or stiffness of joints previously involved or involvement of joints not previously affected	A—Reduce 25% B—Reduce 75% C—Reduce 95% or omit one dose
2 Delayed Focal	Improvement lasting 2–4 days followed by symptoms of no 1	A—Reduce 25% B—Reduce 75% C—Reduce 95% or omit one dose
3 General	General malaise, increased fatigue, lassitude, drowsiness, restlessness, chills (with or without elevation of temperature), nausea, headache, eye symptoms, vomiting, palpitation, precordial pain, premature contractions, nervousness, loss of weight, diarrhea, increased sweating, dizziness, mental depression, etc	A—Reduce 50% B—Reduce 75% C—Reduce 75%
4 Delayed General	Improvement lasting 2–4 days followed by symptoms of no 3	A—Reduce 50% B—Reduce 75% C—Reduce 75%
5 Both Focal and General	Both symptoms of no 1 and no 3	A—Reduce 50% B—Reduce 75% C—Reduce 95% or omit one dose
6 Delayed Focal and General	Improvement lasting 2–4 days followed by symptoms of no 1 and no 3	A—Reduce 50% B—Reduce 75% C—Reduce 75%
7 None	No apparent effect from vaccine	Increase 10%
8 Beneficial	Improvement lasting several days	Increase 10% or repeat

The following grades are applicable to all the above reactions

A—Mild
B—Moderate
C—Severe

According to this outline we begin with 10 to 20 organisms and increase the dose by 10 per cent for the first few doses. If the patient pro-

CHART II
The Type of Chart Employed in the Arthritis Clinic to Record the Response to Each Injection
The data recorded indicate the response to treatment obtained in Case V

Name S B	Chart No 12327													
	Address													
Date 1932	9-20	9-27	10-4	10-11	10-18	10-25	11-1	11-8	11-15	11-22	11-29	12-6	12-13	12-21
Temperature	98.4	98.6	98.2	98.4	98.6	98.2	98.8	98.5	98.2	98.4	98.6	98.4	98.2	98.6
Pulse	110	108	106	106	110	108	104	106	104	102	100	90	94	92
Weight	114	114	114	115	114	115	115	116	118	115	116	118	120	121
Blood Pressure	150-80												130-80	
Occupation	None	None	None	None	None	None	None	None	None	None	None	None	None	None
Working	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Fatigue	++	+	+	+	+	+	++	+	+	+	+	++	+	+
Drowsiness	++	+	+	+	+	+	++	+	+	+	+	+	+	+
Insomnia	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Dermatitis	No	No	No	No	No	No	+	No	No	No	No	+	No	No
Headaches	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eyes	Heavy	Same	Same	No	No	No	Heavy	+	+	+	+	+	+	+
Dizziness	No	No	No	No	No	No	+	No	No	No	No	No	No	No
Int Infection	No	No	No	No	No	No	+	No	No	No	No	No	No	No
Emotional	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Nervousness	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nausea	No	No	No	No	No	No	+	No	No	No	No	+	No	No
Vomiting	No	No	No	No	No	No	+	No	No	No	No	No	No	No
Elimination	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD	1 OD
Palpitation	No	No	No	No	No	No	+	No	No	No	No	No	No	No
Precord Pain	No	No	No	No	No	No	\\	\\	\\	\\	\\	\\	\\	\\
Toes	\\	\\	\\	\\	\\	\\	\\	\\	\\	\\	\\	\\	\\	\\
Metatarso-Phalangeal	\\	\\	\\	\\	\\	\\	\\	\\	\\	\\	\\	\\	\\	\\

/ Pain, \ Tenderness, - Swelling, | Redness, ⊕ Grating, ○ Heat, × Stiffness, R Right, L Left

gresses satisfactorily, no effort is made to increase the dose more rapidly. If there is improvement, the same dose is frequently maintained over a long period of time. If, after several injections have been given, the patient's condition remains stationary, that is, if there is an indefinite response, the dose is increased rapidly, e g from 15 to 25 per cent. If, after increasing it in this manner, a dose is found on which the patient improves, the procedure mentioned above is followed. If improvement is not obtained in this way it is best to reduce the dose to one-tenth or one-twentieth of the initial dose and proceed according to chart 1. In some cases a greater percentage of increase may be tolerated but it may often lead to a severe focal reaction, the patient may become markedly worse and it may require one or two months to repair the damage. (See Case II.) We, therefore, do not recommend an increase of over 25 per cent at any time. If a reaction occurs, the dose must be reduced according to its severity. (See chart 1.) In some cases we have observed that one or more joints have been improved, while others have become worse. In these instances, the dose is reduced until no untoward reaction is obtained in the most hypersensitive joint and the procedure outlined in chart 1 is followed.

In the recent cases the weather has been recorded on a chart with space for temperature, barometric pressure, humidity, and atmospheric conditions and our observations of the reactions have been modified by these reports. The adoption of the above measures has enabled us to obtain the maximum degree of improvement with the minimum of unfavorable reactions. The following case report (Case V) illustrates the response to treatment based on the above procedure.

CASE V

A strain of viridans with an agglutinin titer of 1:10,240 was recovered from the throat of a patient with arthritis. An initial dose of 50 organisms was given, which was followed by a favorable response. This was repeated several times and then increased on an average of 15 per cent each time. On one occasion, when the dose was increased 25 per cent (from 80 to 100 organisms), there was a definite focal reaction. The maximum dose given this patient was 100 and the average was 60 organisms. Definite improvement was obtained as shown by chart 2. At the beginning of treatment, there was a marked involvement of most of the joints of the body, whereas, after 14 weeks of treatment, there remained only swelling and stiffness in the hands and fingers. (See chart 2.) The patient had gained eight pounds in weight, the constitutional symptoms were markedly improved and she was able to carry on her household duties without difficulty. The sedimentation rate at the beginning of treatment was 65 mm per hour. At the end of 14 weeks it was reduced to 35 mm per hour (a drop of 30 mm). The basal metabolic rate at the beginning of treatment was plus 16 and at the end of 14 weeks it was plus 17. This case illustrates the results obtained with the procedure outlined in this paper.

ANALYSIS OF 100 CASES

In the above series, we have used the classification adopted by the New York clinics. (See chart 3.)

CHART III

Classification of Arthritis and Allied Conditions

1 ARTHRITIS

Group 1 (Infectious)

- a Arthritis of rheumatic fever (Synonym Rheumatic disease)
- b Rheumatoid arthritis (Synonyms
 - 1 Chronic infectious arthritis
 - 2 Atrophic arthritis
 - 3 Proliferative arthritis
 - 4 Marie-Strumpell disease and Still's disease)
- c. Arthritis caused by known specific microorganism (Named according to etiologic organism)

Group 2 (Degenerative)

Osteoarthritis (Syn Hypertrophic arthritis, including Heberden's nodes and malum coxae senilis)

Group 3 (Allergic)

Serum sickness

Group 4 (Traumatic)

Includes occupational injuries, loose cartilages, sprains, etc. (Named according to joint involved)

Group 5 (Metabolic)

- a Gout
- b Scurvy
- c Rickets
- d Ochronosis

Group 6 Neurogenic arthropathy (Including Charcot's joint, posthemiplegic etc)

Group 7 (Mixed)

Includes any combination of the above

Group 8 (Unclassified)

- a Any arthritis of uncertain type
- b Any arthritis not included in the above

2 ALLIED CONDITIONS

Named according to etiology, if known, and anatomical part involved

- a Bursitis
- b Neuritis
- c Myositis
- d Fascitis
- e Myofascitis

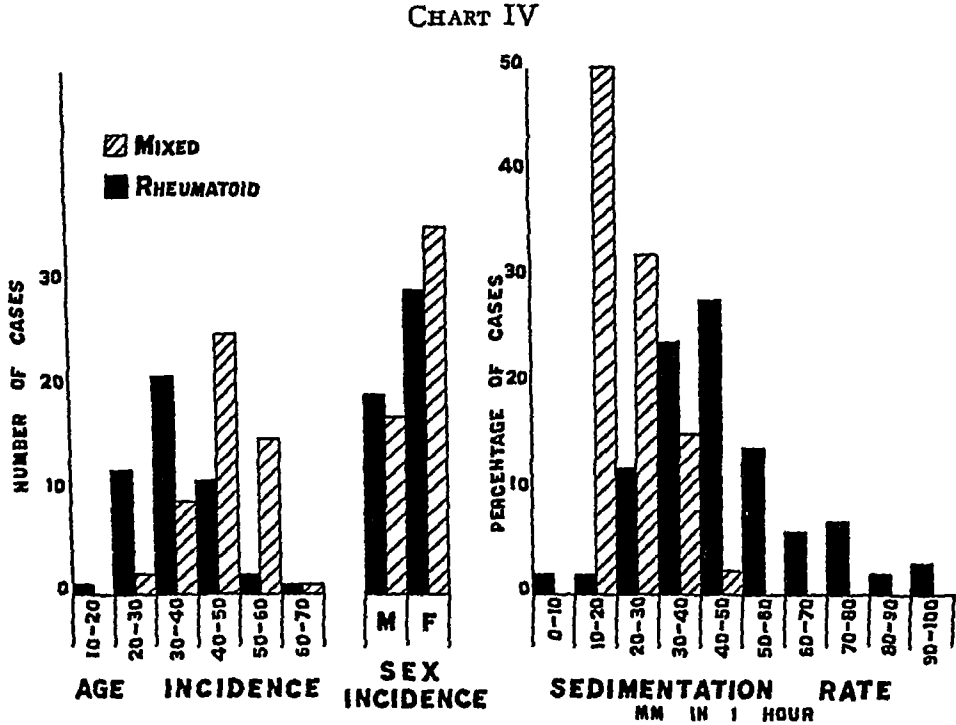
(Example Bursitis, traumatic, right subdeltoid)

In the rheumatoid group, we have included only those cases showing the typical, bilaterally symmetrical, spindle-shaped swelling of the second phalangeal joints of the fingers. There were a large number of cases showing a polyarthritis of long duration which is frequently classed as rheumatoid arthritis, but they showed evidence of other factors and we believed that they should be placed in the mixed group. This accounts for the relatively large number of cases of mixed arthritis in this series. There were 48 of the rheumatoid type and 52 of the mixed.

Age Incidence The rheumatoid group occurred with increasing frequency from the early part of the second decade, reaching its maximum in the middle of the third decade, whereas, the mixed group occurred with increasing frequency from the middle of the third decade, reaching its maximum in the middle of the fourth. (See chart 4)

Sex Incidence In our series, both types of arthritis were more frequent in females than in males. (See chart 4)

Sedimentation Rate The highest sedimentation rate was found in the rheumatoid group, 84 per cent having a sedimentation rate of 30 mm or more per hour (Westergren technic) The mixed group gave a lower rate, 26 (50 per cent) being between 10 and 20 mm , 16 (32.5 per cent), between 20 and 30 mm , 8 (15.2 per cent), between 30 and 40 mm ; and 2 (2.2 per cent) above 40 mm (See chart 4)



Our findings agree with previous reports that the sedimentation rate is higher in rheumatoid arthritis and is proportional to the activity of the disease

Blood Counts Numerous counts were done on a large number of patients to determine the effect, if any, of the intravenous administration of vaccine on the red, white and differential blood counts In order to determine the normal in relation to meals, time of day, etc the patients' diets were standardized and a number of counts made each hour of the day before vaccine therapy was instituted The same procedure was followed after the administration of vaccine and compared with the average for the same time of the day There was no significant difference (See chart 5)

Duration of the Disease The maximum was 16 years, the minimum, three months, and the average, three years

Joints Involved The principal difference in the findings of the two types of arthritis was in the greater frequency of involvement of the fingers, hands and mandible in the rheumatoid group In both types the knees, ankles, wrists, hands, shoulders, feet and fingers were more frequently involved. It is also of interest to note the frequency of involvement

of the cervical and lumbar spine (see chart 6) and to note that the initial symptoms frequently occurred in the cervical spine

CHART V
Blood Counts
Average Blood Counts Before Vaccine Therapy *

Time of Day,	R B C	W B C	Hgb per cent	Differential (per cent)			
				Polys	Lymph	Mono	Eos
9 a m	4,450,000	7,100	80	58	33	6	3
10 a m	4,300,000	7,000		56	34	6	4
11 a m	4,180,000	7,750		60	32	6	2
12 a m	4,700,000	7,950		58	30	9	3
1 p m	4,540,000	7,250		58	28	11	3
2 p m	4,400,000	7,400		60	31	8	1
3 p m	4,150,000	6,800		54	38	6	2
4 p m	4,310,000	6,650		52	38	7	3
5 p m	4,400,000	6,100		54	34	10	2

Average Blood Counts After Vaccine Therapy †

Time of Day	Interval after Vaccine	R B C	W B C	Hgb per cent	Differential (per cent)			
					Polys	Lymph	Mono	Eos
10 a m	1 hr	4,300,000	7,350	80	56	33	7	4
11 a m	2 hrs	4,280,000	7,150	78	54	35	8	3
12 m	3 hrs	4,440,000	7,000	83	58	30	8	4
1 p m	4 hrs	4,650,000	6,800	80	55	33	9	3
2 p m	5 hrs	4,460,000	7,600	79	59	32	8	1
3 p m	6 hrs	4,320,000	7,400	82	52	40	8	1
4 p m	7 hrs	4,200,000	8,300	83	55	34	6	1
5 p m	8 hrs	4,400,000	8,000	84	51	37	8	4
6 p m	9 hrs	4,320,000	7,800	82	56	33	7	4
9 a m	24 hrs	4,530,000	6,800	85	52	39	7	2
3 p m	30 hrs	4,640,000	8,000	83	58	34	5	1
9 a m	48 hrs	4,400,000	7,800	84	56	35	7	2
3 p m	54 hrs	4,530,000	8,300	89	57	34	6	3
9 a m	72 hrs	4,310,000	7,400	83	53	38	7	2
9 a m	90 hrs	4,400,000	6,800	77	59	31	8	2
9 a m	120 hrs	4,700,000	8,300	79	55	36	8	1

* Counts were made hourly during the daytime for four days The figures given represent the average for each hour, based on a study of 25 patients

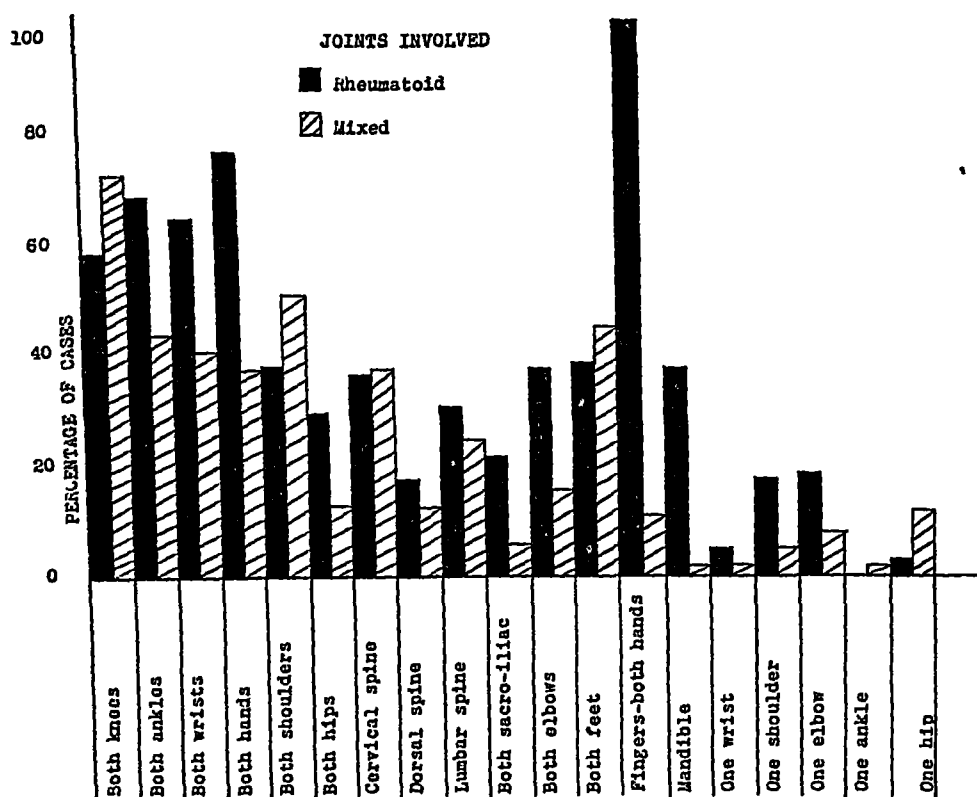
† Similar observations were made and extended over a period of five days after each dose

Foci No foci were removed in this group after treatment was instituted and all those mentioned below had previously had some form of treatment without apparent benefit

There were 33 patients who had previously had teeth extracted, with improvement in six cases (18 per cent), 30 had had tonsils removed with improvement in three (10 per cent), six had had cholecystectomies with improvement in three (50 per cent), four had had gynecological operations with no improvement, four had received massage for an infected prostate

with improvement in one (25 per cent) This makes a total of 90 patients who had previously had foci removed or treated, with improvement in 18 (20 per cent)

CHART VI



An effort should be made to remove foci of infection but this alone is insufficient to effect a cure After-treatment is necessary to obtain maximum improvement

TREATMENT

In the rheumatoid group, the longest period of treatment was 22 months, the shortest, four months, the average, 10 months

In the mixed group, the longest period of treatment was 20 months, the shortest, four months, the average, nine months

The injections were usually given twice weekly The dose was never very high in any case, the highest single dose given being 10 millions; the lowest, 10 organisms, and the average, from 500 to 2,000. Many patients did not receive more than 500 organisms at any time No other medication was given

RESULTS

In order to appraise the results obtained, it was necessary to establish criteria on which to base conclusions We adopted the following (1) reduction in pain, swelling and stiffness with increase of function; (2) lessening of any deformities, (3) improvement in constitutional symptoms,

and (+) lowering of the sedimentation rate. As previously mentioned consideration was given to variations of the weather and most of the group were observed during both winter and summer months. An effort was made to determine the percentage of improvement, based upon the above criteria, and any patient with less than 25 per cent improvement was considered unimproved.

Of the rheumatoid group (48 cases), 39 (81.35 per cent) were improved and nine (18.65 per cent) were unimproved. Of the mixed group (52 cases), 40 (77 per cent) were improved and 12 (23 per cent) were unimproved. Of the total number of cases studied, 79 per cent were improved and 21 per cent unimproved. These results were obtained with patients who had had arthritis for a considerable time. In another series of patients with a shorter duration, we have obtained a higher percentage of improvement. Improvement was in general inversely proportional to the duration of the disease.

DISCUSSION

It became apparent from weekly observations over a period of several years, that natural remissions in rheumatoid and mixed arthritis were much less frequent than in rheumatic fever. When present, they were evanescent in character. Although this constancy of symptoms is unfortunate for the patient, it is a valuable aid in the interpretation of the effects of any type of treatment. Therefore, we chose for this study patients with rheumatoid or mixed types of chronic arthritis which had run a chronic course and was either at a standstill or was growing progressively worse. It is unwise to suggest a fixed dosage to be used in all cases. The routine procedure as outlined in chart 1 was used merely as a working basis, a starting point from which one must deviate according to individual variations. The percentage increase in dosage which may be tolerated by different patients is extremely variable. This phenomenon may be explained in part by the difference in the sensitivity of each patient and partly by the degree of specificity of the vaccine used. The persistence of foci of infection will tend to maintain a degree of hypersensitiveness which interferes with the progress of vaccine therapy and retards improvement. In cases presenting an extreme sensitivity to the autogenous vaccine and in which it is impossible to obtain improvement, a "hidden" focus of infection should be sought.

In the beginning, we attempted to increase the dose as rapidly as advocated by other workers but, as previously mentioned, this produced unfavorable reactions. We believe that better results are obtained by maintaining a small dose over a long period of time.

Since we began this work, the proportion of patients who have been given vaccines intravenously has steadily increased. More than 300 patients with chronic arthritis (rheumatoid and mixed types) of all grades of severity have been treated by the above methods. Although improvement

has not occurred in all, the results have been far more satisfactory and encouraging than with other methods of treatment which we have used.

SUMMARY AND CONCLUSIONS

1 Patients with rheumatoid or mixed types of chronic arthritis were treated by the intravenous administration of vaccines under suitably controlled conditions. The antigens used consisted of phenolized, unheated, autogenous strains of streptococci having high agglutinin titers with the patients' own serums.

2 Repeated small doses of vaccine given intravenously tend to desensitize the patient.

3 A plan for the general administration of such vaccines has been outlined. This can be followed in ambulatory patients with little danger of causing unfavorable reactions.

4 We have been unable to increase the dosage as rapidly as other authors have advocated.

5 We have purposely avoided the term "cure." We believe it rash to make such a claim until patients have been followed over a prolonged period.

6 Improvement has been obtained in 79 per cent of the cases.

7 We believe these results warrant further studies along similar lines.

Our thanks are due to Mr George H Chapman of the Clinical Research Laboratory for his cooperation in working out the bacteriologic and serologic studies described in this paper.

REFERENCES

- 1 Poynton, F J, and PAYNE, A. Researches on rheumatism, 1913, Macmillan Company, London.
- 2 Roserow, E C. Etiology of arthritis deformans, preliminary note, Jr Am Med Assoc, 1914, lxii, 1146.
- 3 Moon, V H, and EDWARDS, S R. Results of blood cultures in rheumatoid arthritis, Jr Infect Dis, 1917, xvi, 154-161.
- 4 Billings, F, COLEMAN, G H, and HIBBS, W G. Chronic infectious arthritis: statistical report with end-results, Jr Am Med Assoc, 1922, lxxviii, 1097-1105.
- 5 BURBANK, R, and HADJOPOULOS, L G. Serologic significance of streptococci in arthritis and allied conditions, Jr Am Med Assoc, 1925, lxxxiv, 637-641.
- 6 FORKNER, C E, SHANDS, A R, JR, and POSTON, M A. Synovial fluid in chronic arthritis, bacteriology and cytology, Arch Int Med, 1928, xlii, 675-702.
- 7 CICH, R L, NICHOLLS, E E, and STAINSBY, W J. Bacteriology of blood and joints in chronic infectious arthritis, Arch Int Med, 1929, xliii, 571-605.
- 8 CICH, R L, NICHOLLS, E E, and STAINSBY, W J. Etiology of rheumatoid arthritis, Am Jr Med Sci, 1931, clxxvi, 12-25.
- 9 SMITH, J C. Role of streptococci in rheumatic diseases, Jr Lab and Clin Med, 1929, xiv, 1144-1156.
- 10 DAWSON, M H, OLNSTEAD, M, and BOOTS, R H. Studies on etiology of rheumatoid arthritis, bacteriological investigations on blood, synovial fluid and subcutaneous nodules in rheumatoid arthritis, Proc Soc Exper Biol and Med, 1931, xxviii, 419-420.
- 11 HADJOPOULOS, L G, and BURBANK, R. Correlation of experimental streptococcal arthritis in rabbits with chronic rheumatoid arthritis, Jr Bone and Joint Surg, 1932, xiv, 471-500.

- 12 COATES, V, and COOMBS, C F Observations on the rheumatic nodule, Arch Dis Child-
hood, 1926, i, 183-193
- 13 MENZER, A Serumbehandlung bei acutem und chronischem Gelenkrheumatismus, Ztschr
f klin Med, 1902, xlvii, 109-152
- 14 SWIFT, H F Rheumatic fever, Am Jr Med Sci, 1925, clxx, 631-647
- 15 SWIFT, H F, DERICK, C L, and HITCHCOCK, C H Rheumatic fever as manifestation
of hypersensitiveness (allergy or hyperergy) to streptococci, Trans Assoc Am Phys,
1928, xliii, 192-202
- 16 SWIFT, H F, DERICK, C L, and HITCHCOCK, C H Bacterial allergy (hyperergy) to
nonhemolytic streptococci, Jr Am Med Assoc, 1928, xc, 906-908
- 17 SWIFT, H F Rheumatic fever, Hektoen lecture, Billings Foundation, Jr Am Med
Assoc, 1929, xcii, 2071-2083 (With full review of literature)
- 18 ZINSSER, H Significance of bacterial allergy in infectious diseases, Bull New York
Acad Med, 1928, iv, 351-383
- 19 ZINSSER, H, and YU, H Bacteriology of rheumatic fever and allergic hypothesis, Arch
Int Med, 1928, xlii, 301-309
- 20 ANDREWS, C H, DFRICK, C L, and SWIFT, H F The skin response of rabbits to non-
hemolytic streptococci I Description of a secondary reaction occurring locally after
intradermal inoculation, Jr Exper Med, 1926, xlv, 35-53
- 21 DERICK, C L, and SWIFT, H F Reactions of rabbits to nonhemolytic streptococci,
general tuberculin-like hypersensitiveness, allergy or hyperergy following secondary
reaction, Jr Exper Med, 1929, xlix, 615-636
- 22 SWIFT, H F, and DERICK, C L Reactions of rabbits to nonhemolytic streptococci,
skin reactions in intravenously immunized animals, Jr Exper Med, 1929, xlix, 883-
897
- 23 DERICK, C L, HITCHCOCK, C H, and SWIFT, H F Reactions of rabbits to nonhemolytic
streptococci, study of modes of sensitization, Jr Exper Med, 1930, lii, 1-22

XANTHOMA ACCOMPANIED BY HYPERCHOLESTEROLEMIA, OCCURRING IN AN OTHERWISE NORMAL INDIVIDUAL, AND IN AN INDIVIDUAL WITH ACROMEGALY AND DIABETES *

By THOMAS HODGE MCGAVACK, A B , M D , and H CLARE SHEPARDSON, A B , M A , M D , F A C P , *San Francisco, California*

THE STUDY of fat metabolism, and of the rôle it plays in the animal economy, has been diligently pursued by many investigators, especially in recent years. As a result of this impetus, lipid metabolism, and particularly cholesterol utilization, is being investigated constantly in a great variety of pathologic conditions.

Alteration in the normal utilization of the lipid substances is found ordinarily as a complicating condition in some more profound disease process, although it may occur spontaneously. However, regardless of the etiology of such disturbance, the accumulation of the lipids in the organism frequently acts as a morbid factor, the effects of which may ramify to distant parts of the body.

Disseminated xanthomatosis, exclusive of xanthoma palpebrarum is an unusual manifestation of disturbed fat metabolism resulting from an infiltration of lipid substances into the skin and other tissues. It may occur either as a complication, usually of diabetes mellitus, or as an idiopathic condition. It is a rare disease as is evidenced by the fact that of 18,400 consecutive medical admissions to The Johns Hopkins Hospital, xanthomas were found in only 3 instances.¹ It should be added, however, that treatment of the disease does not usually require hospitalization. Bloch² collected and analyzed 96 cases of the disease and these represent all of the idiopathic type appearing in the literature to 1931, in which blood cholesterol determinations have been made. Wile³ has recorded all of the known instances of familial xanthoma involving 14 families and including 42 patients.

Xanthoma diabeticorum is also rare. In 1924, Major⁴ reported 3 cases and reviewed 71 others previously appearing in the literature. We have appended a chronologically arranged list of the 23 cases reported since that time,⁵ bringing the total number of known diabetic xanthomas to 97.

The concomitant occurrence of acromegaly and diabetes mellitus has been well established,^{6, 7, 8} although disseminated xanthomatosis complicating such a condition has been recorded in but two instances^{9, 10}. In both of these, as in the second case here reported, the acromegaly had preceded by some time the onset of the diabetes.

While xanthomatous tumors have been known to occur in the absence of elevated blood cholesterol values,^{11, 12, 13, 14} and indeed in the presence of

* Received for publication March 20, 1933.

From the Department of Medicine and the Metabolic Clinic, University of California Medical School, San Francisco, California.

values as low as 44 mg per cent,¹⁵ hyperlipidemia and hypercholesterolemia are decidedly the rule. Ingiam¹⁰ observed low values for cholesterol in seven out of 58 cases studied, but Wile, Eckstein and Cuitis¹² and also Rowland¹⁷ have suggested that the xanthomatous lesions make their appearance only in the presence of an hyperlipidemia, low lipid values subsequently may be obtained although the tumor nodules remain unchanged. They believe, "that a disordered fat metabolism in which cholesterol undoubtedly plays a part as a constituent of the body lipoids is responsible for xanthoma." Bloch² and Schaaf¹¹ have presented evidence showing that disturbance in the normal proportionate relationship between the various lipoids of the blood (cholesterol, cholesterol esters, phosphatides, fatty acids, neutral fats and soaps) is the determining factor for their deposition in the blood and tissues, "All the lipid constituents with the exception of soaps are insoluble in water. Consequently they do not exist in the serum in a dissolved form, but in that of a finely dispersed stable emulsion. The normal proportion of all the lipid constituents must be maintained in the blood, in order that they should fulfill their proper function. The proportions, which normally exist between the lipid constituents of the blood and between these substances and the albumin of the serum, constitute the best index of the stability of this complex emulsion. If the proportion is changed considerably in any direction, i.e., if the amount of any, or several, of these constituents is altered, the result, according to the laws of colloidal theory, is a disturbance in the stable aqueous, lipid emulsion, the blood serum. A disproportion of this kind leads to a coarsening of the lipid particles in the emulsion, and in the higher degrees to separation and finally precipitation of individual constituents in the tissues—in a word, to xanthomatous lesions." Rowland,¹⁷ Leites,¹⁸ Weber,¹⁹ and Jaffe²⁰ all conclude that the production of xanthoma results not merely from a passive "supersaturation" precipitation, but rather from an active process in which the reticulo-endothelial system plays an essential rôle. The absorptive and secretive power of this system for cholesterol has been shown to vary with changes in its physiochemical state¹⁸ so that, "All the varied xanthoma manifestations can be brought back to a single pathologic principle, the reticulo-endothelial system is infiltrated by certain substances."¹⁷

The typical xanthoma cell is a reticulo-endothelial cell infiltrated with lipoids. The lipid disturbance is apparently primary,^{21, 22, 23} a fact which may explain why xanthomatosis is most commonly associated with diseases such as diabetes, nephritis, and obstructive jaundice in which there is likely to be an increased blood cholesterol.^{20, 21, 24, 25, 26} Deposit in the reticulo-endothelial tissues is secondary. However, as Weidman²⁷ points out, "Some factor in addition to the mere presence of hypercholesterolemia and young connective tissue cells is necessary to the development of xanthoma tuberosum." Other contributing factors in the formation of these unusual nodules mentioned by various writers and of interest in connection with the cases here described include the duration of the blood condition, trauma,²³ local vascular supply^{17, 22} and local or systemic infection^{17, 28}

CASE I

E W, an American, male, carpenter, aged 27, entered the clinic September 19, 1931, complaining chiefly of a papular eruption on the palmar surfaces of his hands as well as other parts of his body. His only other complaint was the infrequent occurrence of abdominal distention and gaseous eructations after meals. His family history was unimportant and lacked any example of a dermatosis similar to his own. His personal anamnesis included measles and whooping cough in childhood, appendicitis (operated) at the age of 17 years, and a Neisserian infection of six to seven weeks' duration at the age of 18 years. His present troubles began about two years



FIG. 1 Case I Lesions about the elbows as they appeared in November 1931

prior to entry with slight pain on kneeling and the simultaneous appearance of papular, grouped lesions over both knees. Within the next six months similar nodules appeared on the palmar surface of both hands and about the elbows. Within the last six months, papules have appeared over the buttocks and along the entire posterior surface of the thighs. The lesions are painless although discomfort results from such irritation as pressure. The abdominal distress after meals had been noted for several years, was intermittent in character, and occurred usually after eating highly seasoned or 'greasy' foods. His diet consisted essentially of meats and starches, few green vegetables were included. It is particularly interesting that he has never liked or eaten butter or other fats. Coffee and tea were rarely used, he customarily drank two or six pints of home-brewed beer daily.

Physical examination revealed a well developed man weighing 72 kg (158 4 pounds) and measuring in height 162 5 cm (5 feet, 5 inches) Abnormal findings were confined to the skin, which displayed firm, papular and nodular, yellow to saffron-colored lesions distributed over the extensor surfaces of both elbows, both knees, the buttocks and the posterior aspects of both thighs, in the palms of both hands and on the fingers (figures 1 and 2) These lesions varied in diameter from 2 mm to 1½ cm, being smallest on the thighs and palms of the hands and largest about the elbows and knees



FIG 2 Case I Lesions in the palms of the hands as they appeared in November 1931

Laboratory findings The urine had a specific gravity of 1,019, sugar and albumin were absent The sediment contained only the normal constituents The fasting blood sugar was 110 mg per cent A sugar tolerance curve showed the following levels after the ingestion of 100 grams of glucose Fasting, 105 mg per cent, one-half hour, 122 mg per cent, one hour, 115 mg per cent, two hours, 98 mg per cent The fasting (14 hours) blood plasma cholesterol was 1075 mg per cent (average of two determinations on a single specimen) The carbon dioxide combining power of the plasma was 53 1 volumes per cent The blood plasma chlorides were 556 mg per cent, the non-protein-nitrogen 38 9 mg per cent, the urea nitrogen 17 1 mg per cent Cholecystography by the oral method revealed a normally functioning gall-bladder The rose bengal test for liver function was normal, showing 55 per cent excretion of the dye in the first eight minutes, and an additional 33 per cent in the second eight minute period Results of the blood count were red blood cells 5,450,000, hemoglobin (Sahli) 98 per cent, white blood cells 7,650, polymorphonuclear neutrophils 71 per cent, eosinophiles 3 per cent, basophiles 1 per cent, small lymphocytes 18 per cent, large lymphocytes 6 per cent The basal metabolic rate was minus 6 1 per cent Roentgen-rays of the skull, chest, feet and legs showed no evidence of bony change, nor did the vessels of the extremities appear sclerosed

Course This is summarized in chart 1 On an ordinary diet from September

CHART I
Summary of Findings in EW (Case I)

Date	Weight in lbs	Diet				Blood cholesterol in mg per cent			Medication	Remarks
		CHO	Prot	Fat	Cal	Whole	Plasma	Esterin Plasma		
9-21-31	158.1		General				1075		None	Glucose tolerance curve low Blood chemistry normal (see text) Low cholesterol diet B M R 6.1% minus
10-20-31	158.0	350	70	General	2490		742		"	
11-4-31	—			90			605		"	
11-10-31	—	"	"	"	"		464		"	Digestive symptoms worse 4 egg yolks added to daily diet. Has had mild bronchitis Egg yolks discontinued B M R 3.0% minus B M R 2.1% minus Fasting blood sugar 0.81% States has dieted carefully B M R 2.1% minus
12-3-31	156.5	"	"	"	"		757		"	
12-29-31	—	"	"	"	"		476		"	
1-16-32	—	"	81	110	2714		445		"	
1-23-32	—	"	"	"	"	375	510	219	"	
2-1-32	157.0	"	"	"	"		432		"	
3-5-32	—	"	70	90	2490		568		Insulin U-40 daily	
3-9-32	—	"	"	"	"		610		Insulin U-60 daily	
3-12-32	—	"	"	"	"		472		"	
3-16-32	—	"	"	"	"	298	456		"	
3-27-32	—	"	"	"	"		470		"	Insulin stopped Thyroid gr. ii daily Thyroid gr. v daily
3-29-32	—	"	"	"	"		406		"	
4-5-32	—	"	"	"	"	320	402		"	
4-19-32	155.0	"	"	"	"	309	455		"	
5-10-32	155.0	"	"	"	"		500		"	
5-17-32	153.6	"	"	"	"					
7-5-32	148.5	"	"	"	"	287	357			
8-27-32	151.0	"	"	"	"	439	629	321		
9-19-32	151.5	"	"	"	"					

19, 1931 to October 22, 1931, the patient's blood plasma cholesterol fell from 1075 mg per cent to 742 mg per cent. On the latter date his dietary regime was changed to a high carbohydrate, low fat, low cholesterol diet (CHO 350 gm, P 70 gm, and F 90 gm). This was continued until January 16, 1932, at which time a definite softening of all of the skin lesions could be noted. The blood plasma cholesterol had receded to 445 mg per cent. The gastrointestinal symptoms remained unchanged. Four egg yolks daily were then added to the diet. Two weeks later, the plasma cholesterol was 430 mg per cent. Because of the obvious lack of effect of the additional egg yolks on the cholesterol content of the blood and because of the patient's dislike for eggs, the latter were discontinued. Pending an opportunity to hospitalize the patient no further changes were made in his regimen until March 5, 1932. He entered the University Hospital on this date. From then until May 10, 1932, 60 units of insulin were administered daily. During this period the blood plasma cholesterol varied from 568 mg per cent to 402 mg per cent. Thyroid substance (Armour's desiccated) was started early in May, and the dose gradually increased until in three



FIG 3 Case I Lesions about the elbows as they appeared in January 1933. Very marked reduction in number and size of xanthoma.

weeks the patient was receiving 5 grains daily. This dosage has been continued to date (October 15, 1932) with but four pounds loss of weight. No change in pulse rate and no elevation in the metabolic rate have occurred—the most recent determination being 21 per cent minus on September 19, 1932. The blood plasma cholesterol has fluctuated from 500 mg per cent at the beginning of the period through a low point of 357 mg per cent in July to a present (October 15, 1932) value of 629 mg per cent. From the beginning of the administration of the high carbohydrate, low fat diet there has been a gradual but definite recession of the lesions, most marked in the period of thyroid administration. All of the lesions are softer and less rounded

About the elbows especially, recession is associated with a change of the nodular condition to one of scale or crust formation. When the crusts drop or are pulled away, they expose an area of approximately normal skin, surrounded by a very faint erythematous zone. Many of the lesions in the hands and about the elbows have entirely disappeared (Figures 3, 4, and 5)

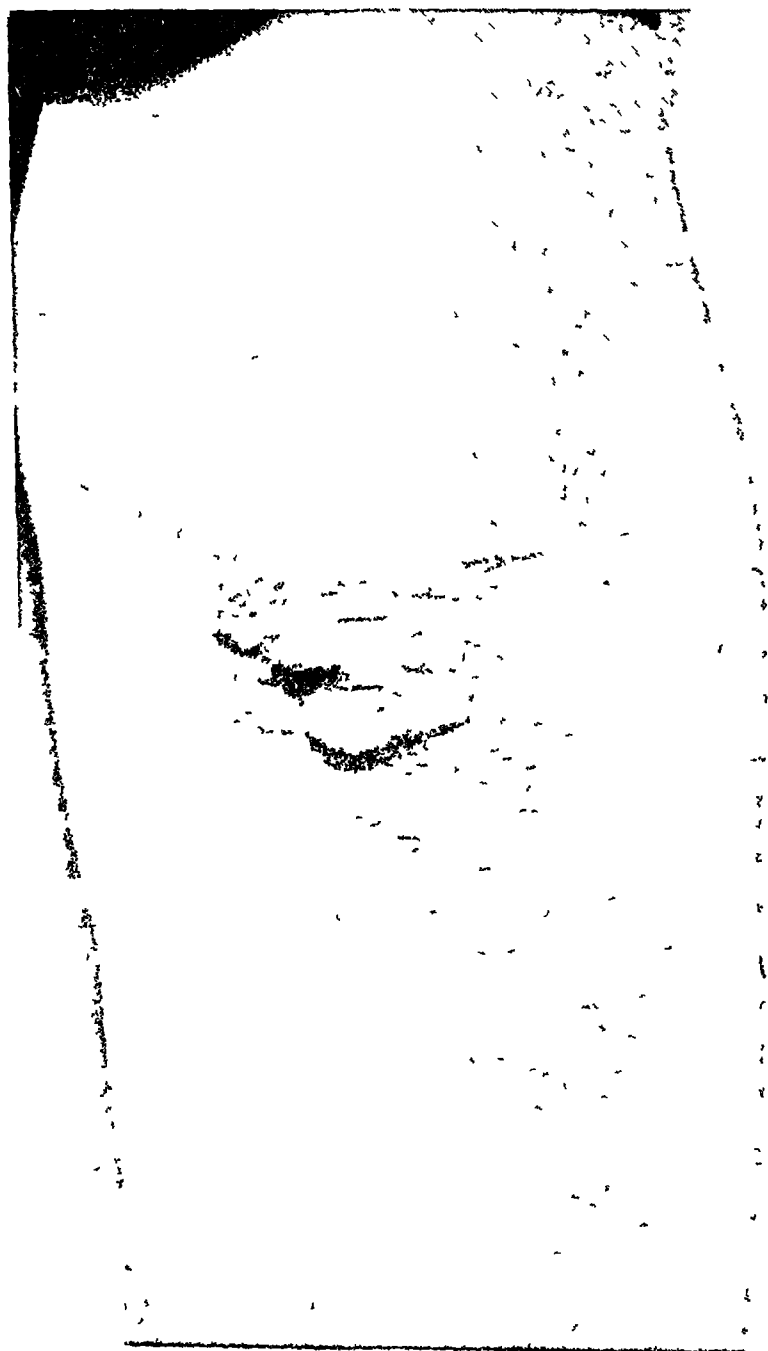


FIG. 4. CASE I. Taken in January 1933. Lesions about the elbows are fewer in number and much softer.

CASE II

W. A., a 33 year old single negress first reported to the clinic October 5, 1928, complaining of generalized weakness, amenorrhea and blurring of vision. A de-

creasing and irregular menstrual cycle—her earliest symptom of ill health—made its appearance at the age of 24 years. One year later complete amenorrhea supervened and has persisted. At the age of 30 years, she noticed a disturbance of vision and when fitted for glasses, found it “difficult to get a sufficiently wide frame.” She

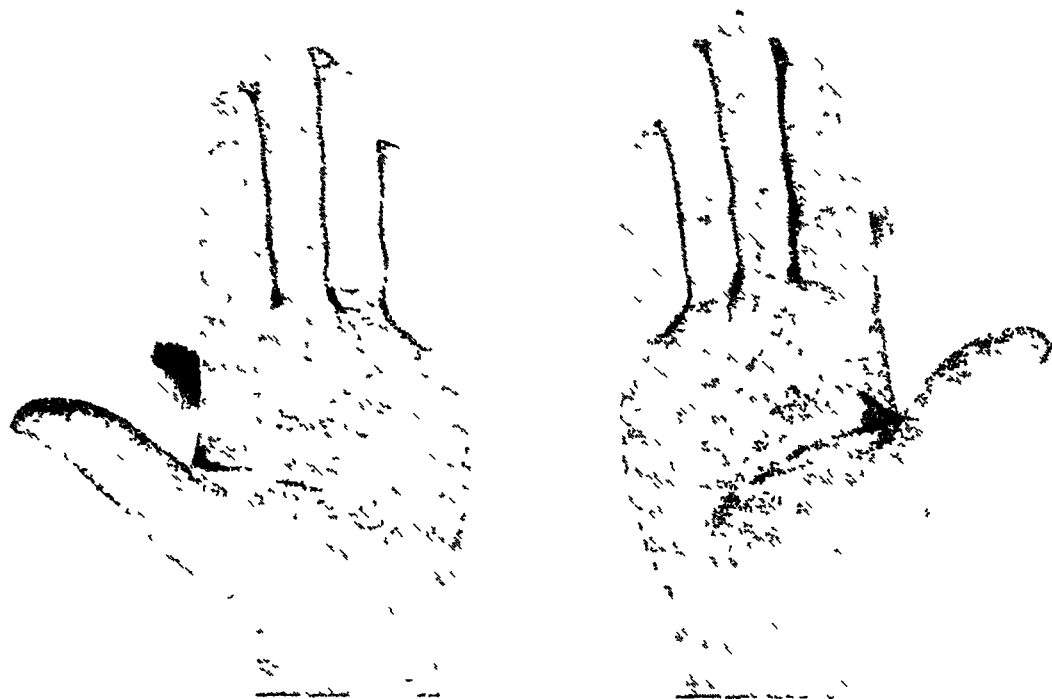


FIG 5 Case I Taken in January 1933 Xanthoma have disappeared from palms of hands

began to require progressively larger gloves and shoes. Three months before coming to the clinic, at 33, polyphagia and polydipsia (but not polyuria) made their appearance. She became increasingly irritable, suffered from severe frontal headaches, noctidrosis, and generalized asthenia.

Physical examination (see figure 6) at that time revealed an individual whose appearance was typical of acromegaly. The brow was low and wide with wrinkled folds of skin and prominent frontal bossae. The eyes were widely separated with puffy upper lids, widened palpebral apertures and a suggestion of exophthalmos. There was a bilateral external strabismus. The pupils were regular, round and dilated. The right responded to light but not to accommodation, the left to neither light nor accommodation. Vision in the right eye was 20/70, using a plus two lens. Light perception was questionable in the left eye. Fundal examination revealed a well advanced optic atrophy on the left side. There was no choking of either disc. Perception in the left eye was too poor for perimetric field determinations but the right eye showed complete blindness over the temporal half of the fundus. The nose and lips were wide and thick, the malar prominences slightly flattened. Marked prognathism was apparent. The incisor teeth were widely spaced, the tongue was huge, wide and long. Hair distribution was normal. The thyroid gland was normal. Heart and lungs were normal but the bony thorax was enlarged. Blood pressure was 110 systolic and 85 diastolic. No abnormalities were noted in the abdomen. The hands and feet were broad and long. The fingers were flat and wide without the normal taper (Figure 9). The toes were similarly shaped. There was slight cervico-dorsal kyphosis. The skin was swarthy with freckles, thick but smooth.

Laboratory procedures revealed a negative Wassermann, a basal metabolic rate of 41 per cent minus, glycosuria and a definitely lowered sugar tolerance (See chart 2) The blood count was normal. Roentgen-ray of the skull evidenced "a marked enlargement of the sella turcica with thinning of the anterior and posterior clinoid processes and depression of the floor" (See figure 6) Roentgen-rays of the hands and feet showed "some clubbing of the distal phalanges but practically no enlarge-



FIG 6 Case II Photograph and roentgen-ray taken in October 1928, nine years after the first symptoms of pituitary disease were noted. Low brow with wrinkled skin folds, wide separation of eyes, external strabismus, prognathism. Note the large sella turcica with erosion of anterior and posterior clinoid processes. Roentgen-ray findings in 1932 are essentially like those shown here.

ment of the bones from sub-periosteal bone. There is an exostosis in the same place on both great toes. There are defects in the bone of the terminal phalanges of the thumb at corresponding points, and of the left fifth digit about the proximal interphalangeal joint" (Dr. Stone).

At this time a diagnosis was made by Dr. Hans Lissner of pituitary tumor resulting in acromegaly with amenorrhea, possibly hypophyseal diabetes and optic atrophy.

Course. A transphenoidal hypophysectomy was done October 23, 1928, by Dr. Fleming, from which recovery was uneventful. Microscopic examination of the excised tumor showed it to be a chromophilic adenoma. Within the two weeks immediately following operation, four roentgen-ray treatments—each representing one-half of a skin erythema dose—were given to the hypophyseal region. Subsequent to operation headache and noctidrosis promptly disappeared. There has been steady improvement in eyesight, as was noted by comparing the perimetric fields taken just prior to operation, in October 1928, with those taken in May 1932. Visual acuity of the right eye has improved from 20/70 to 20/40, and of the left eye from almost complete blindness to 20/120.

The persistence of glycosuria and hyperglycemia despite steady improvement in other symptoms usually ascribed to pressure about the hypophyseal region, finally necessitated a diagnosis of true diabetes mellitus. Quantitative care of that condition was begun in May 1929. Management of the diabetes, unfortunately complicated by a pulmonary abscess, necessitating hospitalization for five weeks in May and June 1929, has been difficult although supposedly the patient has been on only barely more than a basal diet throughout her illness. Abstracts from her record, found in chart 2, give some suggestion of the difficulties encountered.

CHART II
Summary of Findings in W A (Case II)

Date	Wt in lbs	Daily Diet				Insulin Daily Units				Blood sugar tolerance curve in mg per cent				Four period urine				Blood cholesterol			B M R	Remarks
		CHO gm	Prot gm	Fat gm	Cal					Fasting	1/4 hour	1 hour	1 1/2 hours	1st	2d	3d	4th	Whole mg %	Plasma mg %	Hrs af- ter food		
10-6-28	140.5					0				110	200	217	206	Green	Green	Olive	Olive				-4 1%	
11-6-28						0				93	207	256	210	Blue	Green	Yellow	Olive				-1 5%	13th day after hypophysectomy
2-9-29						0				330	523	530	555	Orange	Orange	Orange	Red					Respiratory infection
5-14-29	135.5					0				268				Single specimen								Entered Hospital for lung abscess
6-14-29		100	90	110	1750	40				70	185	287	200	Single specimen							-15 2%	Convalescing from lung abscess
8-14-29	125.0					?								Orange	Orange	Orange	Orange					Has not dieted carefully or used insulin regu- larly First visit to Diabetic Clinic
9-4-29	128.3	100	80	80	1440	30								Blue	Yellow	Olive	Blue					
9-20-29	130.2					35				333	551	650	544	Red	Olive	Red	Yellow				+0.9%	
10-1-29	132.4					40								Blue	Green	Green	Blue					
10-14-29	135.0					50				180	333	444	284								-2 1%	
10-23-29						52								Blue	Green	Blue	Blue					
12-4-29	138.2					68				472				Red	Red	Olive	Yellow					Had 4 x-ray tta to hypophysis Nov 1-8 each 1/2 SED Weighing diet carefully Some head- ache since beginning x-ray
3-21-30	131.6					0				333	-2 1/2	hours	p c	Single specimen							-21.0%	Acetone ++ Duocetic acid + No insulin since Jan 1, 1930 Has not attended Clinic in that time.
4-11-30	133.0	100	60	100	1540	50								Blue	Green	Blue	Blue					
12-8-31	142.0	130	70	90	1610	50								Green	Green	Olive	Green					Has been fairly well controlled on diet noted 4-11-30 and insulin ranging from 40-50 U daily, effects of high CHO diet to be tried
4-12-32	140.4					55				384	-2 1/2	hours	p c	Green	Green	Green	Green	1150	2 1/2			Blood plasma milky and thick.
7-10-32						55				377	-1 1/2	hours	p c	Olive	Olive	Olive	Olive	803	1 1/2			Xanthoma appeared 5 weeks ago
7-20-32	145.0	200	75	40	1400	60								Orange	Green	Blue	Blue					X-rays of skull negative to xanthomatous changes
8-30-32						60								Blue	Blue	Blue	Blue	555	725	2	-1 3%	
9-20-32	144.0					70				307	-1 1/2	hours	p c	Green	Green	Green	Green					Xanthoma condition improved

From about January 1, 1930, to March 21, 1930, the patient did not follow the prescribed regime. She was admitted to the hospital on the latter date in coma. After relieving the acidosis, a basal metabolic rate of 21.9 per cent minus was obtained. Daily administration of one grain of desiccated thyroid substance (Armour's) was continued throughout the ensuing year with return of the metabolic rate to approximately normal.

From the time the patient was placed on a diabetic regime in May 1929, to October 15, 1932, her tolerance for carbohydrate has increased only about 25 gm daily. Traces to appreciable amounts of sugar have been found in the urine from



FIG 7 Case II Xanthomatous lesions about the elbows as they appeared in July 1932

time to time. While the fasting blood sugar has at times been within normal range, it is usually elevated, and all post-prandial determinations have revealed a marked hyperglycemia. In view of these facts, effort was made in April 1932, to determine the state of the blood lipoids through blood cholesterol determinations. Blood withdrawn three hours after the morning meal April 12, 1932, showed a *glucose content of 387 mg per cent and total plasma cholesterol 1150 mg per cent*. The plasma was very thick and milky. For four months prior to this determination, the patient had been taking a moderately high carbohydrate diet (CHO 130, P 70, F 90, Cal 1610), upon which she was allowed to remain. About June 1, 1932, discrete yellowish to salmon colored nodules of from 2 mm to 15 mm in diameter began to make their appearance over the entire trunk and extremities. (See figures 7, 8, 9.) These were most numerous and tended to coalesce in the palms of the hands, at the elbows and on the knees. On July 19, 1932 her post-prandial (1½ hour) blood sugar was 377 mg per cent and the plasma cholesterol 893 mg per cent. In an effort to improve the xanthomatous condition which had grown steadily worse, a still higher carbohydrate

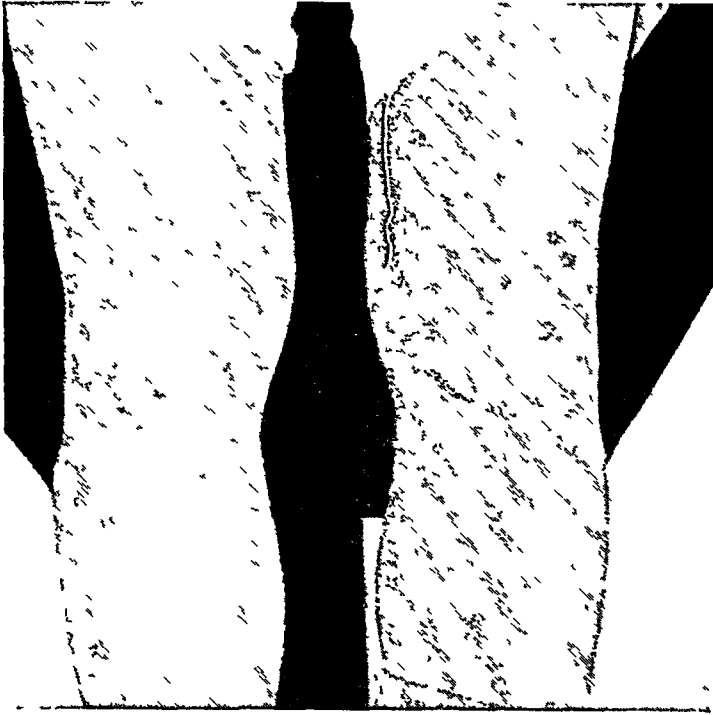


FIG 8 Case II Xanthomatous lesions about the knees as they appeared in July 1932

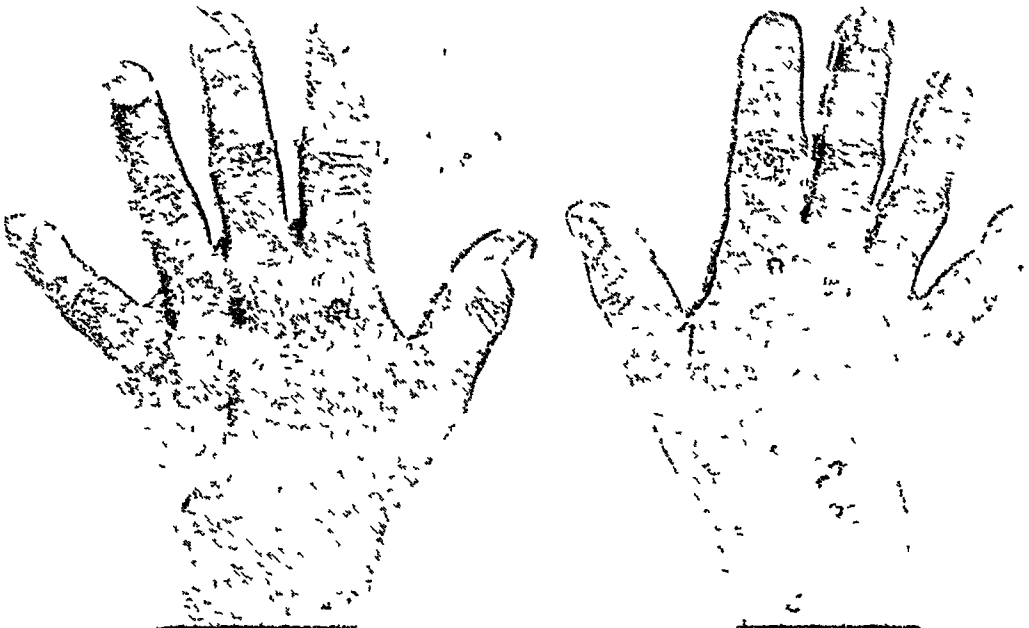


FIG 9 Case II Xanthomatous lesions on dorsum of hands as they appeared in July 1932 Photographs indicate the most marked localizations of the nodules Isolated tumefactions were scattered over the trunk, arms and thighs similar to those appearing on the right wrist in this photograph Note the flat, wide fingers without the normal taper

and extremely low fat, low cholesterol diet (CHO 200, P 75, F 40, Cal 1460) with appropriate insulin dosage was prescribed. At the present time (October 15, 1932), the blood plasma cholesterol has been further lowered to 725 mg per cent, some of the lesions on the thighs have disappeared, leaving behind them pigmented scars



FIG. 10 Case II Xanthoma about elbows have almost disappeared and have been replaced by small pigmented scars, January 1933

The remaining lesions have decreased in size and are more flattened in appearance. Those in the palms have ceased to cause discomfort when using the hands. (Figures 10, 11, 12)

DISCUSSION

In the first of the two cases here reported, the fact that the xanthoma (and probably the hypercholesterolemia) had been present for at least two years may be responsible for the slowness in involution of the cutaneous lesions, as well as the difficulty in maintaining lowered blood cholesterol values. It is reasonable to suppose that Case II with pituitary disease of at least nine years' duration, and later profound disturbances in carbohydrate metabolism, evidenced alterations in blood fat long before cutaneous phenomena appeared, at least, the highest recorded cholesterol was noted two months prior to their onset.

Local trauma, consequent upon riding horseback and driving a car may

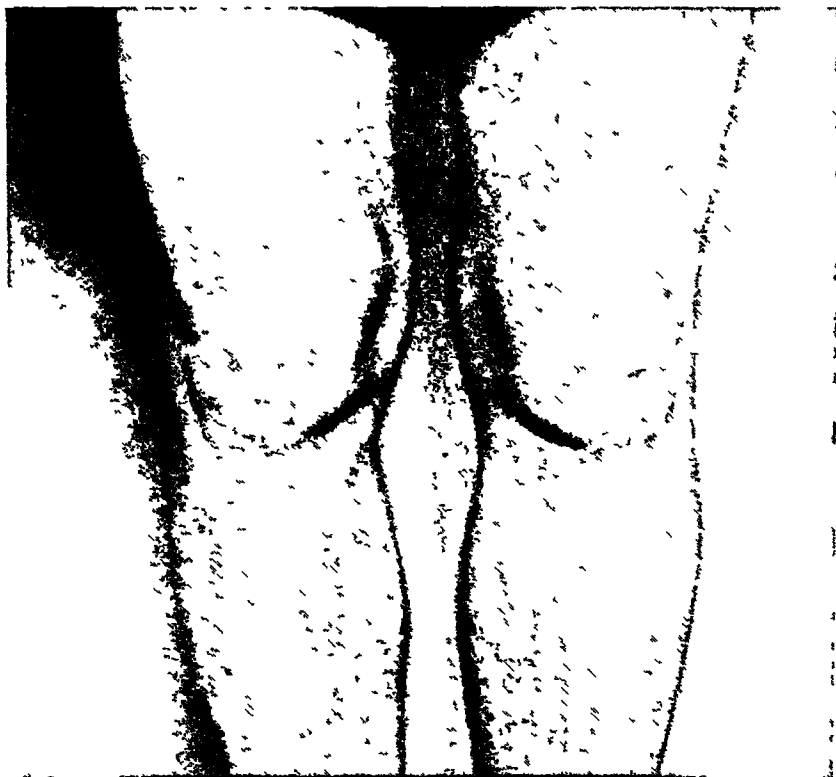


FIG 11 Case II Pigmented areas are the only residual evidence of the xanthomatous lesions about the knees, January 1933

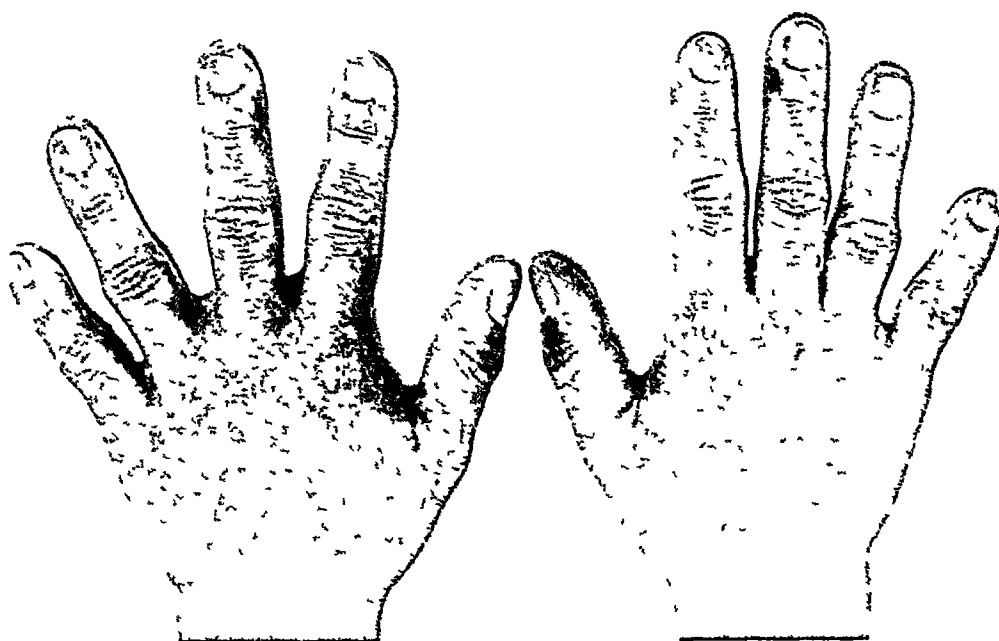


FIG 12 Case II Small pigmented scars indicate location of previous xanthoma, January 1933

have predetermined the eruption of many nodules along the thighs and over the buttocks in the non-diabetic case presented. It cannot possibly account for the location of the other lesions, nor do the lesions of the diabetic patient with acromegaly suggest trauma as a factor in their distribution.

It is difficult to link the onset of cutaneous nodules with infection, local or general, in Case II, for, although she had several minor respiratory infections in the spring of 1932, none occurred within five weeks prior to the appearance of the skin tumors.

The internal secretions may play a part in xanthomatosis. Rony and Mortimer,²⁹ however, have failed to find any effect upon artificially produced lipemia in dogs as a result of the administration of the following substances: insulin, pituitrin, suprarenalin, thyroid substance, parathormone, secretin, cholecystokinin, bile salts. Their work involved short experimental periods as well as a hyperlipemia independent of endogenous disease, a factor which undoubtedly plays a rôle in the lipid disturbances associated with pathologic states. In contrast to their findings, the weight of clinical evidence suggests positive effects from some of these substances under certain conditions. It has been shown repeatedly that variation in the activity of the thyroid gland will materially alter cholesterol metabolism^{26, 30, 31, 32, 33, 34, 35, 36, 37}. Low blood cholesterol values usually supervene when an excess of thyroid is available, and high values when a deficiency exists. Storage of cholesterol in the reticulo-endothelial cells is decreased by thyroid administration.³⁷ The iodine number of the plasma fatty acids is elevated in hyperthyroidism.³³ Improvement but not total disappearance of lesions has been noted in hypothyroidism with xanthomatosis following the administration of thyroid substance together with a fat free diet.³⁸ Favorable results in other non-diabetic xanthoma following the use of thyroid extract have also been reported.^{39, 40}

In our non-diabetic patient with xanthoma, the effects of thyroid administration have been only suggestive although the cutaneous manifestations have involuted more rapidly and steadily than under any other form of treatment. The diet, amply adequate for the work performed, has been kept constant for the past eight months, thus eliminating exogenous factors. The acromegalic individual had very moderate doses of desiccated thyroid substance (1 gr Armour's daily) for approximately one year following the low basal metabolic test in March 1930. No positive association between the xanthomata and the activity of her thyroid gland has been observable.

Although Chamberlain⁴¹ found no changes in blood plasma cholesterol following the administration of pituitary extract and although storage of cholesterol by the reticulo-endothelial system is not altered (histologic evidence) by "solution of pituitary gland,"³⁷ Moehlig and Ainslee⁴⁰ have shown the existence of a definite relationship between abnormalities of the pituitary gland itself and fat metabolism. Furthermore Ralli⁹ calls at-

tention to the decreased carbohydrate tolerance which many acromegalic patients exhibit, as well as to the incidence of true diabetes mellitus and the associated alteration in fat metabolism, occurring with acromegaly. Both Muller²⁶ and Franchini⁴³ have reported an increased excretion of cholesterol in the feces in acromegaly.

Apparently then it must be assumed from the work of various investigators that retention of the lipid substances usually is associated with increased pituitary activity. Furthermore the chronological order of events in our Case II makes it reasonable to suppose that the primary disturbance in metabolism is to be found in the pituitary gland. The secondary manifestation, namely, true diabetes mellitus, as attested by the repeatedly high blood sugar tolerance curves, even after relief of all pressure symptoms in the region of the hypophysis, appeared much later. Lipemia and finally xanthomatosis accompanied the hyperglycemia.

Insulin influences fat metabolism through the close association of the latter with carbohydrate utilization in the body. Thus it has been shown that artificial hyperlipemia in depancreatized dogs disappears more rapidly when insulin is administered.²⁰ Also it has been suggested^{44, 45, 46} that insulin inhibits gluconeogenesis from fat, while Rony and Ching⁴⁷ have demonstrated that alimentary lipemia may be prevented by feeding carbohydrate with the fat, or by giving insulin. These latter workers conclude that the passage of sugar into the blood facilitates the passage of fat, and this has been confirmed by showing that insulin has a definite influence upon the fixation of cholesterol in the tissues^{37, 48}. However, investigations dealing with the effects of insulin on blood cholesterol have produced contradictory results, for certain workers^{41, 49} have found a reduction of an increased, but not of a normal blood cholesterol level subsequent to the administration of insulin. Also clinically, rapid reduction and disappearance of xanthomatous lesions and of hyperlipemia have been observed to follow the exhibition of insulin in the diabetic form of xanthomatous disease,^{4, 50, 51, 52} whereas in non-diabetic forms, even in the presence of hyperlipemia, insulin seems valueless.^{11, 16, 38}

In the case of non-diabetic xanthoma discussed in this paper, insulin exerted no apparent beneficial effect although the experimental period of four weeks may have been too short to warrant definite conclusions. On the other hand, the dosage of insulin used was as high as was compatible with the welfare of the individual. Moreover, no abnormality of carbohydrate metabolism is patent in this case. Abnormal carbohydrate metabolism apparently results in changes in fat utilization, the converse is not necessarily true. Steady clinical improvement of the xanthomatous nodules as well as the hypercholesterolemia has followed the use of insulin in the second case recorded, but further observations are necessary to bespeak any permanent relief from the therapy instituted. However, Rowland²¹ regards the prognosis of xanthoma diabeticorum poor as to the permanent disappearance of the cutaneous manifestations and unfavorable as to life expectancy.

Mattick and Reinhard⁵³ have shown that patients receiving roentgen-ray or radium radiation of cancerous lesions develop low blood cholesterol values. Healing of the cholesterol bone condition in the Schuller-Christian syndrome by roentgen-ray therapy but inability to prevent the appearance of new lesions has been noted^{17, 28}

The diabetic acromegalic mentioned in this report received two series of roentgen-ray treatments to the hypophyseal region, which may have delayed the onset of xanthomatosis. At least the time interval between the onset of the acromegaly and the development of the cutaneous nodules was much longer than in the cases of Ralli and of Noothoven¹⁰

Diet in non-diabetic xanthoma, and diet with insulin in the diabetic type probably offers the best therapeutic procedure at our disposal, although Rowland²¹ suggests that such treatment concerns itself with the hypercholesterolemia, rather than with the causative factor of generalized fat disturbance. Muller²⁶ has reported a temporary postprandial increase in the blood cholesterol of both carnivorous and omnivorous animals but notes that "a permanent increase does not depend upon food itself." Furthermore, Hunt⁵⁴ and Blix⁵⁵ found no influence upon the blood cholesterol values of controlled diabetic patients subsequent to the feeding of foods with a high cholesterol content. Probably the endogenous metabolism of cholesterol in the main is independent of the exogenous supply. But this apparently holds true only within certain limits for other workers have been able to lower or raise blood cholesterol values in man and in animals by sufficiently prolonged low or high fat diets^{56, 57, 58, 59}. A statistical report from Joslin's clinic⁶⁰ suggests that the average blood plasma cholesterol is lower than in clinics where high fat diets are allowed. From the clinical viewpoint, low caloric diets have proved necessary to bring about an involution of cutaneous xanthomata and a reduction of the hyperlipemia^{3, 12, 50, 61}. Wile, Eckstein and Curtis¹² have succinctly remarked that "the best treatment for this affection in the presence or absence of glycosuria would seem to be a reduction diet, treating the condition as one would obesity."

In both cases here recorded low fat, low cholesterol diets have been prescribed. In Case I, the calories are ample for light work. The basal metabolism remains normal regardless of the ingestion of five grains of desiccated thyroid (Armour's) substance daily. The xanthomatous nodules are gradually but steadily disappearing (figures 3, 4, 5), despite the fluctuating blood cholesterol. Such a course is in apparent contrast to other cases in which low caloric equivalents, with or without thyroid extract, were necessary to cause involution. The diabetic patient with xanthoma has been placed on a diet of approximately a basal maintenance caloric requirement. Clinical improvement is obvious in the xanthomatous lesions (figures 10, 11, 12), but carbohydrate metabolism has not yet approached normal levels. It has been impossible to hospitalize her recently and the suspicion

remains that she either consciously or unconsciously ingests more food than prescribed

The unusually high initial cholesterol values found in these patients (1075 and 1150 mg per cent, respectively) are of especial interest and for that reason were in each case repeatedly checked. The method of total cholesterol estimation was that of Bloor,⁶² and for free cholesterol that of Bloor and Knudson.⁶³ As far as we have searched the literature, only two instances of higher values are found. Engman's⁵⁰ patient with diabetic xanthoma had a blood plasma cholesterol of 1,800 mg per cent (normal value by the method used, 300 mg per cent). Bloor⁶⁴ records a case of diabetic lipemia without xanthoma in which the blood plasma cholesterol was 1,370 mg per cent (estimation by Bloor's original method, 1916). Brown and Howard¹ found a value for serum cholesterol of 1,000 mg per cent in a non-diabetic patient with disseminated xanthoma (method not mentioned). In Rowland's^{17, 21} cases the highest figures for plasma cholesterol in xanthomatosis were just under 600 mg per cent.

In the two patients here described the low whole blood cholesterol determinations, as contrasted with those for plasma cholesterol, show the tendency of the red corpuscles to maintain a constant cholesterol content in spite of marked changes in the plasma. This is nicely exemplified in Case I, in which roughly calculated values for cholesterol in the corpuscles have been well within the normal range, despite the high plasma cholesterol. In this connection Mayer and Schaeffer⁶⁵ have suggested that the corpuscles of the blood behave more or less as tissue cells, that is, have a fairly constant composition in contrast to the blood plasma. It is evident, however, that this ability of the corpuscles to maintain a normal cholesterol content is not complete, as the red cells in an "emergency" can also be "loaded" with fat and phospholipid^{26, 64}. Such storage of lipoids in the corpuscles apparently exists in our second patient.

Because a disturbance in the relative proportions of the individual blood lipid bodies has been suggested as a causative factor in xanthomatosis, attempt was made to follow the ester fraction of the blood plasma cholesterol in the first case here described. On two occasions, this was increased in direct proportion to the elevation of the total cholesterol, no conclusions are possible without more frequent analyses.

SUMMARY

1 The incidence of xanthomatosis (excepting the Schuller-Christian syndrome and Niemann Pick's disease) is noted as recorded in the literature.

2 Findings in one case of idiopathic disseminated xanthomatosis, and in one case of acromegaly with xanthoma diabeticorum, are recorded.

3 In the non-diabetic individual, moderately restricted diet and thyroid gland administration have been attended by a partial involution of the xanthomatous lesions. High cholesterol feeding for a short period (two weeks) did not affect the blood cholesterol level. Insulin administration had no obvious effect upon either the blood or cutaneous disturbance.

4 In the acromegalic patient with xanthoma diabeticorum, administration of a high carbohydrate, low fat and low caloric diet with insulin, has been accompanied by some lowering of the hypercholesterolemia and a diminution in the number and size of the skin nodules

5 Features of especial interest are noted (*a*) the rarity of the condition exhibited in the second patient—association of acromegaly, diabetes mellitus and xanthoma diabeticorum, (*b*) the excessively high blood cholesterol values in both cases, (*c*) the low cholesterol content of the blood corpuscles despite very high plasma values

6 Some factors concerned in cholesterol metabolism and in the production of xanthoma are discussed with particular reference to the cases reported

CONCLUSIONS

It is well nigh impossible to make sweeping deductions concerning a condition, the incidence of which is so rare as to preclude observations in a large series of cases. However, the facts here presented seem to warrant the following comments

1 Disturbed carbohydrate utilization is not a necessary antecedent to altered fat metabolism

2 Insulin is without value in the treatment of non-diabetic xanthoma, but is important in the management of the diabetic type

3 Dessicated thyroid substance apparently has a favorable influence upon involution of non-diabetic xanthoma

4 Diets with a reduced fat component and of low caloric equivalents afford the quickest method of causing involution in diabetic and idiopathic xanthomas

REFERENCES

- 1 BROWN, T R, and HOWARD, J T Xanthoma multiplex, with report of case, *Internat Clin*, 1931, iv, 106-113
- 2 BLOCH, B Metabolism, endocrine glands, and skin diseases, with special reference to acne vulgaris and xanthoma, *British Jr Dermat*, 1931, xliii, 61-87
- 3 WILE, U J, and DUEMLING, W W Familial xanthoma, *Arch Dermat and Syph*, 1930, xxi, 642-647
- 4 MAJOR, R H Xanthoma diabeticorum, *Bull Johns Hopkins Hosp*, 1924, xxxv, 27-32, *Med Clin N Am*, 1924, vii, 1059-1064
- 5 The following cases of xanthoma diabeticorum have been reported in the literature since 1924
 - a* MACHLIS, S A D Diabetes mellitus complicated by lipemia retinalis and xanthoma diabeticorum, *Jr Am Med Assoc*, 1924, lxxxiii, 1428-1429 (Complete relief of amaurosis and disappearance of skin lesions under dietary and insulin therapy)
 - b* GORDON, W H, and FELDMAN, M S Report of a case of xanthoma diabeticorum, its response to insulin treatment, question of familial tendency, *Jr Michigan Med Soc*, 1924, xxiii, 231-233 (Entire disappearance of lesions under insulin)
 - c* RATHERY, F, and GOURNAY, J J Xanthoma in syphilis complicated with diabetes mellitus, *Bull et mem Soc med d hôp d Paris*, 1924, xlviii, 1531-1535, abstract *Jr Am Med Assoc*, 1924, lxxxiii, 2120 (Involution under insulin therapy)
 - d*. VAN VLOTEN, W J v B Diabetic xanthoma, *Nederl Tijdschr v geneesk*, 1924,

- ii, 2846-2849, abstract, Jr Am Med Assoc, 1925, lxxxiv, 480 (Reports a case of universally distributed lesions relieved by insulin, cholesterol of the blood also reduced)
- e McDONAGH, J E R Case of xanthoma diabeticorum treated with sulfur derivative of histidine (2-thio-4 (or 5)-amino-methyl-glyoxaline), British Jr Dermat, 1925, xxvii, 30-33 (This patient also had syphilis, the writer reports resolution of skin lesions and improvement of the diabetes under the agent mentioned)
- f CHAUFFARD, A, and BRODIN, P Insulin treatment of diabetic xanthoma, Bull et mem Soc med d hôp d Paris, 1926, l, 1003-1007 (Same case reported by Rathery^o)
- g GOLDSTEIN, E, and HARRIS, J Xanthoma diabeticorum, unusual process of involution, Am Jr Med Sci, 1927, clxxiii, 195-201 (Describes a case in which three types of involution went on simultaneously, in the palms, complete disappearance, at the elbows, coalescence and residual pigmentation, on the legs and thighs, "degenerative changes resulting in extensive scar formation—a process hitherto undescribed")
- h BUSSATI, L Un caso di xantoma diabetico, Gior ital di dermat e sifil, 1927, lxxviii, 396-400 (Not available)
- i BRODIN, P Contribution à l'étude du xanthome, son traitement par l'insuline chez le diabétique, Rev med-chir d mal du foie, 1926, l, 329-334 (Not available)
- j STIBBENS, F H Xanthoma diabeticorum, case report, Calif and West Med, 1928, xxviii, 673 (Resolution of lesions in six weeks under proper dietary and insulin regime)
- k BLOEMEN, J J On xanthomata, illustrated by case of xanthoma diabeticorum, Nederl Tijdschr v geneesk, 1928, l, 132-139 (Eight months' duration, improvement under insulin therapy)
- l PUCHULU, F Xanthoma diabeticorum, causes, value of insulin treatment; three cases, Rev med latino-am, 1928, xiii, 814-824 (Record of three cases under insulin therapy)
- m ELVER, A W, and SCHEPS, M Die Wirkung des Insulins auf die Lipochromamie und die Xanthosis diabetica, Klin Wchnschr, 1929, viii, 300-302 (Two cases showing favorable result under insulin treatment)
- n HERTZ, C R Xanthoma diabeticorum, multiple xanthoma, case, Rev méd del Rosario, 1929, xix, 588-593 (Not available)
- o RALLI, E P Acromegaly with diabetes mellitus and xanthoma diabeticorum, report of case, Arch Int Med, 1931, xlvii, 329-335
- p NOOTHOVEN VAN GOOR, J M, and SCHALY, G A Rare complications of pituitary tumors, generalized diabetic xanthoma, corneal edema with hypercholesterinemia and diabetes, nervous ileus, Nederl Tijdschr v geneesk, 1931, lxxv, 1422-1437
- q TEMPLETON, H J, and CHOURET, E E Xanthoma diabeticorum, report of case, Arch Dermat and Syph, 1931, xxiv, 604-606 (Disappearance of lesions under low caloric diet and insulin, concomitant disappearance of hyperlipemia but not of hyperglycemia)
- r BERETERVIDE, J J, MASOCH, T, and RECHNIEWSKI, C Diabetes, hyperlipemia, y xantomatosis generalizada, Arch argent de enferm d ap digest y de la nutricion, 1932, vii, 227-238 (Not available)
- s WHITE, P, and HUNT, H Cholesterol of blood of diabetic children, New England Jr Med, 1930, ccii, 607-616 (Two cases, high cholesterol in one prior to appearance of the lesions and in the other at the time of their appearance.)
- 6 DAVIDOFF, L M, and CUSHING, H Studies in acromegaly, basal metabolism, Arch Int Med, 1927, xxviii, 673-697
- 7 GRAY, J Case of diabetes mellitus with acromegaly and lipemia, Jr Path and Bact, 1929, xxxii, 71-77

- 8 JOHN, H J Possible relationship between acromegaly and diabetes, *Arch Int Med*, 1926, xxxvii, 489-511
- 9 RALLI, E P Acromegaly with diabetes mellitus and xanthoma diabeticorum, report of case, *Arch Int Med*, 1931, xlvii, 329-335
- 10 NOOTHOVEN VAN GOOR, J M, and SCHALY, G A Besondere Erscheinungen bei Hypophysegeschwulsten (a) Xanthoma diabeticorum generalisatum (b) Hornhautodem mit Hypercholesterinämie und Diabetes (c) Neurologischer Ileus, *Wien Arch f inn Med*, 1931, xxii, 101-126
- 11 SCHAAF, F Der Lipidstoffwechsel (mit besonderer Berücksichtigung der Xanthombildung), *Zentralbl f Haut- und Geschlechtskr*, 1930, xxxv, 1, 193
SCHAAF, F, and WERNER, A J Die Pathogenese der Xanthome Die Beziehungen von Cholesterin-, Phosphatid- und gesamt fettgehalt des Blutes zur Entstehung der Xanthome, *Arch f Dermat und Syph*, 1930, clxii, 217-239
- 12 WILE, U J, ECKSTEIN, H C, and CURTIS, A C Lipid studies in xanthoma, *Arch Dermat and Syph*, 1929, xix, 35-51 Lipid studies in xanthoma, further contribution, *ibid*, xx, 489-500
- 13 ROSENBLUM, J The cholesterol and cholesterol ester content of the blood in xanthoma tuberosum multiplex, *Arch Int Med*, 1913, xii, 395-398
- 14 TURNER, A L, DAVIDSON, J, and WHITE, A C Xanthomatosis some aspects of its blood chemistry and pathology, *Edinburgh Med Jr*, 1925, xxxii, 153-174
- 15 BAAR, H Xanthomatosis without hypercholesterolemia in boy of two and one-half years, *Ztschr f Kinderh*, 1924, xxxviii, 682-687
- 16 INGRAM, J T Xanthomatosis cutis hypercholesterolemia, *British Jr Dermat*, 1927, xxxix, 335-346
- 17 ROWLAND, R S Xanthomatosis and reticulo-endothelial system, correlation of unidentified group of causes described as defects in membranous bones, exophthalmos and diabetes insipidus (Christian's syndrome), *Arch Int Med*, 1928, xlii, 611-674
- 18 LEITES, S Studien uber Fett- und Lipoidstoffwechsel, uber die Rolle des retikulo-endothelialen Systems im Fett- und Lipoidstoffwechsel, *Biochem Ztschr*, 1927, clxxxiii, 391-412
- 19 WEBER, F P Cutaneous xanthoma and "xanthomatosis" of other parts of body—pituitary xanthomatosis,—"xanthomyelomata" of tendon-sheaths, etc—and the "cholesterin diathesis", with bibliography, *British Jr Dermat*, 1924, xxxvi, 335-370
- 20 JAFFE, R H Reticulo-endothelial system, its rôle in pathologic conditions in man, *Arch Path and Lab Med*, 1927, iv, 45-91
- 21 ROWLAND, R S Anomalies of lipid metabolism, 1929, *Oxford Medicine*, vol 4, part 1, p 214 (51)
- 22 HARRISON, G A, and WHITFIELD, A The pathogenesis of xanthomatosis, with report of a case, *British Jr Dermat*, 1923, xxv, 81-92
- 23 OPPENHEIMER, B S, and FISHBURG, A M Lipemia and reticulo-endothelial apparatus, *Arch Int Med*, 1925, xxxvi, 667-681
- 24 EPSTEIN, E Z Cholesterol partition of blood plasma in parenchymatous diseases of liver, *Arch Int Med*, 1931, xlvii, 82-93
- 25 EPSTEIN, E Z Cholesterol of blood plasma in hepatic and biliary diseases, *Arch Int Med*, 1932, i, 203-222
- 26 MULLER, G L Cholesterol metabolism in health and in anemia, *Medicine*, 1930, ix, 119-174
- 27 WEIDMAN, F D, and SUNDERMAN, F W Hypercholesterolemia, normal blood cholesterol figures for man and for lower animals, the approach to the pathogenesis of the xanthomas, *Arch Dermat and Syph*, 1925, xii, 679-690
WEIDMAN, F D Studies in hypercholesterolemia III The approach to the pathogenesis of the xanthomas, *ibid*, 1927, xv, 659-668
- 28 SOSMAN, M C Xanthomatosis (Schuller-Christian's disease, lipid histiocytosis), *Jr Am Med Assoc*, 1932, xcvi, 110-117.

- 29 RONY, H R, and MORTIMER, B Studies on fat metabolism Lipemia induced by intra-venous fat administration, *Endocrinology*, 1931, xv, 388-404
- 30 BING, H J, and HECKSCHER, H Über die Fettmenge des Blutes bei normalen Menschen, *Biochem Ztschr*, 1924, cxlix, 83-89
- 31 BING, H J, and HECKSCHER, H Der Fett-Cholesteringehalt des Blutes bei Patienten mit Morbus Basedowii, *Biochem Ztschr*, 1925, clviii, 403-416
- 32 DENIS, W Cholesterol in human blood under pathological conditions, *Jr Biol Chem*, 1917, xxix, 93
- 33 NICHOLLS, E G, and PERLZWEIG, W A Plasma fats and iodine absorption capacity of fatty acids in hyperthyroidism, *Jr Clin Invest*, 1928, v, 195-204
- 34 MASON, R L, HUNT, H M, and HURTHAL, L M Blood cholesterol values in hyperthyroidism and hypothyroidism—their significance, *New England Jr Med*, 1930, cciii, 1273-1278
- 35 WESTRA, J J, and KUNDE, M M Blood cholesterol in experimental hypo- and hyperthyroidism, *Proc Soc Exper Biol and Med*, 1932, xxix, 677
- 36 LAROCHE, G L Les variations de la cholestérinémie chez les thyroïdiens, *Presse med*, 1929, xxxvii, 268-269
- 37 GOLDZIEHER, M A, and HIRSCHHORN, L Reticulo-endothelial system, influence of hormones, *Arch Path and Lab Med*, 1927, iv, 958-965
- 38 CHRISTIE, J F, LYALL, A, and ANDERSON, T E Case of xanthoma multiplex associated with hypothyroidism, *British Jr Dermat*, 1930, xlii, 429-435
- 39 JAMIESON, R C Xanthoma tuberosum multiplex, *Arch Dermat and Syph*, 1923, viii, 125-126
- 40 MOEHLIG, R C, and AINSLIE, H B Pituitary gland and cholesterol metabolism, *Ann Clin Med*, 1927, v, 772-779
- 41 CHAMBERLAIN, E N Effect of insulin and other endocrine extracts on cholesterol content of tissues, *Jr Physiol*, 1930, lxx, 441-448
- 42 JOSLIN, E P The treatment of diabetes mellitus, 4th ed, 1928, Lea and Febiger, Philadelphia
- 43 FRANCHINI, G Beitrag zum chemischen und histologischen Studium des Blutes bei Akromegalie, *Berlin klin Wchnschr*, 1908, xlv, 1636-1639
- 44 MACLEOD, J J R The fuel of life, experimental studies in normal and diabetic animals, 1st ed, 1928, Princeton University Press, Princeton, New Jersey
- 45 CHAIKOFF, I L, and WEBER, J J Formation of sugar from fatty acids in depancreatized dog injected with epinephrine, *Jr Biol Chem*, 1928, lxxvi, 813-832
- 46 SOSKIN, S Influence of feeding either fat and lipase or lecithin on sugar excretion of depancreatized dogs, *Biochem Jr*, 1929, xxiii, 1385-1390
- 47 RONY, H R, and CHING, T T Studies on fat metabolism, effect of certain hormones on fat transport, *Endocrinology*, 1930, xiv, 355-363
- 48 LOEFER, M, LEMAIRE, A, and TONNET, J La resorption dans les tissus de la cholestérine, *Compt rend Soc de biol*, 1928, xcvi, 100-101
- 49 NITZESCU, I, POPESCU-INOTESTI, C, and CADARIU, I Cholesterol in experimental diabetes, *Compt rend Soc de biol*, 1924, xc, 1067-1069
- 50 ENGMAN, M F, and WEISS, R S Xanthoma diabeticorum treated with insulin, *Arch Dermat and Syph*, 1923, viii, 625-626
- 51 BLOEMAN, J J On xanthomata, illustrated by case of xanthoma diabeticorum, *Nederl Tijdschr v geneesk*, 1928, i, 132-139
- 52 FLANDIN, C, DUCOURTIOUX, and PECHERY Cholestérinémie et glycémie au cours du xanthome, essai du traitement par l'insuline, *Bull Soc franç de dermat et syph*, 1926, xxxiii, 209-216
- 53 MATTICK, W L, and REINHARD, M C Further studies of effect of radiation on blood cholesterol in malignant disease, *Jr Cancer Res*, 1930, xiv, 426-433
- 54 HUNT, H M Cholesterol in blood of diabetics treated at New England Deaconess Hospital, *New England Jr Med*, 1929, cci, 659-667

- 55 BLIX, G Diabetic lipemia, *Acta med Scandinav*, 1926, lxiv, 142-259, abstract, *Jr Am Med Assoc*, 1926, lxxxvii, 1784
- 56 BLOOR, W R Diet and blood lipids, *Jr Biol Chem*, 1932, xcv, 633-644
57. MCCLURE, C W, and HUNTSINGER, M E Studies in fat metabolism, influence on blood lipids of single foodstuffs, *Jr Biol Chem*, 1928, lxxvi, 1-18
- 58 ORLOWSKI, W Recherches sur la cholestérinémie, *Ann d Méd*, 1927, xxii, 286, 473
- 59 GARDNER, J A, and GAINSBOROUGH, H Studies on cholesterol content of normal human plasma, on so-called alimentary hypercholesterolemia, *Biochem Jr*, 1927, xxi, 130, 141, 1928, xxii, 1048-1056
- 60 WHITE, P, and HUNT, H Cholesterol of blood of diabetic children, *New England Jr Med*, 1930, ccii, 607-616
- 61 CURTIS, A C, WILE, U J, and ECKSTEIN, H C Involution of cutaneous xanthomata caused by diets low in calories, *Jr Clin Invest*, 1929, vii, 249-261
- 62 BLOOR, W R The determination of cholesterol in the blood, *Jr Biol Chem*, 1916, xxiv, 227-231
- 63 BLOOR, W R, and KNUDSON, A The separate determination of cholesterol and cholesterol esters in small amounts of blood, *Jr Biol Chem*, 1916, xxvii, 107-112
- 64 BLOOR, W R Lipemia, *Jr Biol Chem*, 1921, xlix, 201
- 65 MAYER, A, and SCHAEFFER, G Recherches sur la teneur des tissus en lipoides (3^e memoire), teneur des tissus en phosphore lie aux lipoides, constance de cette teneur, *Jr de physiol et de path gen*, 1913, xv, 773-788

ULTRA-VIOLET ENERGY, ITS EFFECT AND INTENSITY AT VARIOUS LOCATIONS AND ALTITUDES *

By MELDRUM K WYLDER, F A C P , ROBERT S ROCKWOOD,† B S , M S ,
P H D , and SAMUEL BUDD LIPPINCOTT, A B , M S ,
Albuquerque, New Mexico

WITH direct proof that rickets occurs in the inverse proportion to the amount of ultra-violet energy reaching the child's body, together with the understanding of the fact that these short waves produce their effect by the activation of ergosterol, we may activate the ergosterol in our patient's body or we may activate the ergosterol itself and feed it to the patient. These established facts furnish a foundation for much valuable study.

The work of Hess, Brown, Howland, and Marriott and many others has put severe rickets, the rickets as described by the older authors, almost out of the picture, or at least in the class of preventable diseases. True there are many cases of mild rickets, but the deformity producing type need never be seen if we but use the agencies at our command.

I recall that when I first went to the southwest, almost 30 years ago, I noted the almost complete absence of rickets and discussed it with an elderly physician who had gone west ahead of the railroad, and he said, "Children who live in the open in our sunshine don't have rickets."

This study of the ultra-violet part of the spectrum, first begun with reference to rickets, has uncovered other possibilities of greater value and farther reaching effect.

With Viosterol (the commercial trade name given activated ergosterol, which is only bottled sunshine) we have a means of giving a measured dose. We know that these short waves stimulate calcium and phosphorus metabolism, and perhaps mineral metabolism in general. Competent observers have shown the beneficial effect of this product in parathyroid and in surgical tetany,^{1,2} in hastening the union of fractures,^{3,4} in benefiting acrodynia,⁵ psoriasis,⁶ urticaria,⁷ angioneurotic edema, eczema,⁸ asthma,⁹ and hay fever¹⁰, and in hastening the calcification of tuberculous lesions, thus checking their tendency to spread^{11,12}. Menschel¹³ reports reduction of fever, disappearance of night sweats, increase in weight, formation of scar tissue, lessened tendency to hemorrhage and general improvement in tuberculous patients. In pregnancy, relief of headaches, irritability, fatigue and stimulation of fetal development have been reported^{14,15}. Backaches, headaches, and nervousness accompanying menstruation are said to have been

* Read at the Montreal Meeting of the American College of Physicians, February 6, 1933.

† Dr. Rockwood, who worked out this method, devised this apparatus, and made these observations, died Nov. 23, 1932 before he had completed this study.

materially benefited ^{1, 16}, and shortening of both bleeding and coagulation time has been observed ^{17, 18}. Space will not permit the enumeration of all the benefits that have been reported

We will soon begin to realize that the ultra-violet portion of ordinary sunshine which we use so little in modern life, shutting it out as we do from our homes, our offices and even our automobiles, has claims to be hailed as humanity's greatest boon

In the study of the short wave part of the spectrum, much work has been done. Several different methods are used in making calculations and there is no way of evaluating the results of one method in terms of another

Hill in England has made an extensive study using the acetone methylene blue method. He found that most of the short waves were lost in London, while in country places they were not. He found a reading of 41 in the Alps and the highest reading he obtained at Peppard Oxon was 23

Frawley ²⁰ made observations on the top of the Sierra Nevada's, at Fresno and at Santa Barbara using the acetone methylene blue method. Between the hours of 10 a m and 2 p m he found a fading of 11 units in the Sierra's, 9 units at Santa Barbara and 9 at Fresno. This method takes into account only the total amount of fading over a given period, but does not permit the estimation of the rate at any particular time

Larsen and Godfey ²¹ made a very extensive series of observations near the Pacific coast using the oxalic acid method. They made observations at Riverside, San Francisco, Yakima, Seattle, Hong Kong and Honolulu, all these sites being near the sea and in low altitudes. Their observations ran over a period of several months and they found wide variations on days that were seemingly clear, so much alike that readings might have been expected to be about the same. These variations were probably due to differences in the amount of moisture in the upper atmosphere, which near the sea varies widely. Such stratification of the atmosphere does not perceptibly affect the clearness of the day. Their conclusions were that the short wave energy reaching the earth's surface in these locations varied so widely that in order to estimate intelligently the proper dosage of heliotherapy, observations should be made daily

In its passage through the earth's atmosphere the solar radiation reaching the earth's surface is depleted by two causes: absorption and scattering. The absorption is due to gases which compose the atmosphere, and occurs in portions of the spectrum which are characteristic for each gas. Water vapor and carbon dioxide produce absorption chiefly in the infra-red, oxygen and ozone chiefly in the ultra-violet. In the antirachitic part of the ultra-violet there is a slight absorption by ozone which is nearly constant for all parts of the earth's surface, since the ozone is held in the layer of the atmosphere 30 to 40 miles above the surface of the earth

The scattering of solar radiation can be divided into two parts: that due to dust particles, which is practically constant for all parts of the spectrum; and that due to atoms, molecules and ions of the gases, which is of

much greater importance in the ultra-violet than in the longer wave length regions, since the scattering varies as the inverse fourth power of the wave length

The work we are reporting was done at the University of New Mexico in collaboration with the University of Michigan. In this work a study of the depletion of the solar radiation of a wave length of 3240 angstrom units was made. The selection of this wave length, 3240, was accomplished by means of a system of filters consisting of a Corex A glass filter and two silver films. The Corex A filter has a transmission band which extends from 2500 to 3900 angstrom units, with a broad maximum at 3200, while the silver has a narrow transmission band with a sharp maximum at 3200. These transmissions taken in connection with solar energy give a maximum transmission of energy at 3240. This energy was focused by means of a quartz lens on a four junction bismuth antimony surface thermopile, and the electrical current produced was measured by means of a Leeds and Northrup high sensitivity galvanometer.

The construction of the receiver and a photograph of the equipment set on a heliostat mounting are shown in figures 1 and 2.

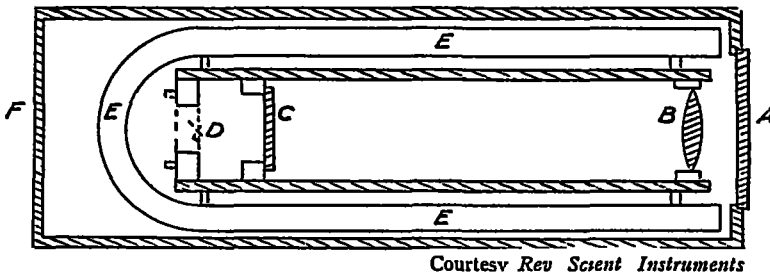


FIG 1 Cross section of receiver (A) silvered Corex filter, (B) quartz lens, (C) silvered quartz plate, (D) thermocouple, (E) Dewar flask, (F) hard rubber case

In this computation the amount of ultra-violet energy of a wave length of 3240 angstrom units is expressed in percentage of the radiation of that length reaching the outer atmosphere, thus if we arrive at a figure of 40 per cent, we mean that 40 per cent of the radiation wave length 3240 is received at the earth's surface and that 60 per cent is lost by absorption and scattering.

The method of computation takes us into higher mathematics and advanced physics and would be too technical for a paper of this nature. With this equipment, observations were made on the campus of the University of New Mexico at an elevation of 5100 feet, on the mesa seven miles east at an elevation of 5800 feet, at Carlito Springs in the Sandia Mountains at an elevation of 6750 feet, and at the Kiwanis Cabin on the crest of the Sandia Mountains at an elevation of 10,300 feet.

At 12 00 noon on the following dates, at the University Station, the readings were as follows

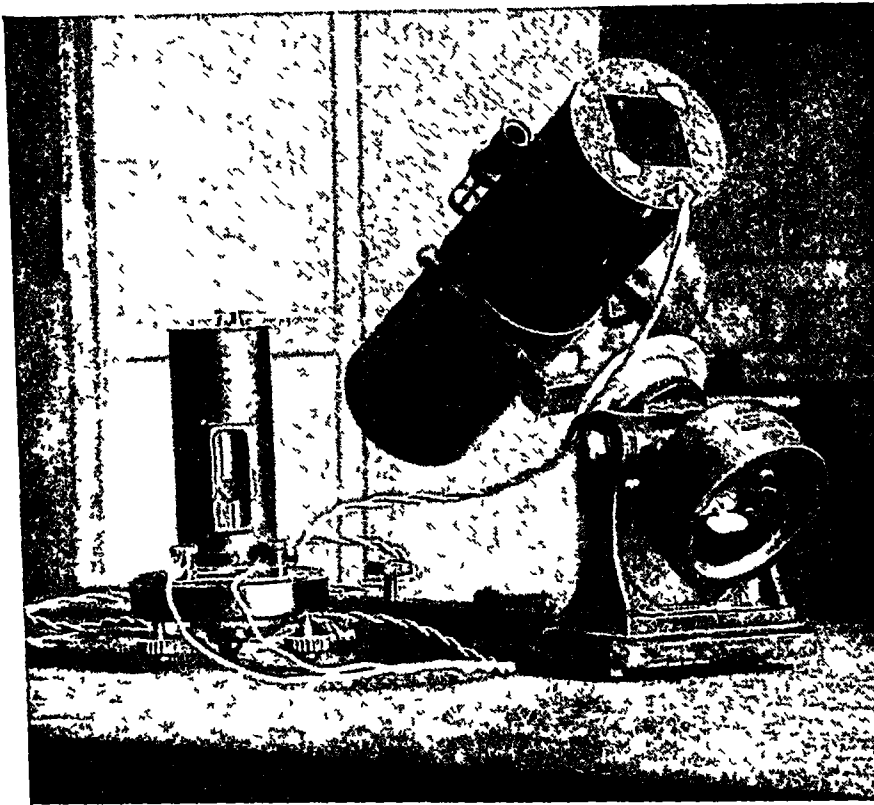


FIG 2 Photograph of apparatus set on heliostat mounting

Oct 17, 1931	33%	Dec 5, 1931	24%
Oct 28, 1931	33%	Dec 11, 1931	23%
Nov 14, 1931	26%	Dec 23, 1931	21%
Nov 25, 1931	24%	Dec 30, 1931	23%
		Jan 18, 1932	25%

This shows the effect of the increasing and decreasing air paths during the winter months

Hourly readings were made at the University, October 28, 1931 from 10 00 a m to 3 00 p m

10 00 a m	28%	1 00 p m	25%
11 00 a m	32%	2 00 p m	21%
12 00 noon	33%	3 00 p m	12%

This shows the effect of the increasing and diminishing air paths as the sun approaches and leaves the meridian

At Sunset View Station, at the mouth of the canyon, elevation 5,810 feet, the readings were as follows

January 8, 1932 from 1 30 p m to 3 30 p m

1 30 p m	30 9%	2 30 p m	21 8%
2 00 p m	27 8%	3 00 p m	18 4%

January 18, 1932 from 11 30 a m to 3 00 p m at same station

11 30 a m	29 8%	1 30 p m	28 6%
12 00 noon	31 0%	2 00 p m	25 5%
12 30 p m	31 7%	2 30 p m	21 3%
1 00 p m	30 3%	3 00 p m	17 4%

At Carlito Springs, elevation 6,850 feet, the following readings were obtained

November 14, 1931 from 10 30 a m to 3 00 p m

10 30 a m	33 9%	1 00 p m	36 3%
11 00 a m	36 3%	1 30 p m	31 4%
11 30 a m	39 2%	2 00 p m	30 5%
12 00 noon	38 8%	2 30 p m	28 0%
12 30 p m	37 7%	3 00 p m	20 7%

It is noteworthy that the highest reading on this day was at 11 30 a m whereas it is usually at 12 30 p m

On December 5, 1931 at Carlito Springs the readings were as follows

11 00 a m	31 9%	1 00 p m	30 3%
11 30 a m	33 9%	1 30 p m	26 4%
12 00 noon	31 9%	2 00 p m	26 8%
12 30 p m	30 7%	2 30 p m	21 1%
		3 00 p m	15 0%

Here again the highest reading was obtained at 11 30 a m and the 2 00 p m reading was higher than the 1 30 p m reading

The following readings were taken at the Kiwanis Cabin on the crest of the Sandia Mountains at 10,300 feet elevation on October 30, 1931 from 10 30 a m to 3 30 p m

10 30 a m	39%	1 00 p m	43%
11 00 a m	40%	1 30 p m	40%
11 30 a m	43%	2 00 p m	35%
12 00 noon	46%	2 30 p m	31%
12 30 p m	47%	3 00 p m	25%
		3 30 p m	16%

and on October 30, 1932 at the same station

10 30 a m	33%	1 00 p m	36 2%
11 00 a m	34%	1 30 p m	34 0%
11 30 a m	36 2%	2 00 p m	29 8%
12 00 noon	39 2%	2 30 p m	26 6%
12 30 p m	40 1%	3 00 p m	21 1%
		3 30 p m	13 8%

The larger percentages at the increased elevation are due to the fact that the light passes through a smaller amount of air, and that there is very little water vapor at these high altitudes, and a negligible amount of dust. The lower readings at the campus show the effect of dust, smoke and water vapor.

On November 5, 1932 the following study was made. An airplane was sent up to an altitude of 12,000 feet, flying over the vicinity in which observations were being made on the ground. Beginning at 11 45 an estimate of the amount of moisture in the air was made at each 1,000 foot level as the airplane descended, using the dry and wet bulb thermometers. This took only three minutes at each level so that very little time was lost between readings. A reading was also taken on the ground. From this data we calculated (using Rockwood's²² formulae), the per cent of transmission one might expect at different altitudes. The calculations gave results as follows:

5,000 feet	27 3%	9,000 feet	37 6%
6,000 feet	30 6%	10,000 feet	39 3%
7,000 feet	32 7%	11,000 feet	41 5%
8,000 feet	35 5%	12,000 feet	42 8%

A direct determination from the ground, altitude 5,050 feet, gave a reading of 29 0 per cent. Only one direct reading was taken because the observer was especially interested in the infra-red determinations during the flight.

We also calculated the per cent of transmission one might expect at the different altitudes if the air were dry, with the following results:

5,000 feet	35 3%	9,000 feet	40 7%
6,000 feet	36 7%	10,000 feet	42 1%
7,000 feet	38 1%	11,000 feet	43 4%
8,000 feet	39 4%	12,000 feet	44 7%

By comparing these results we find at 5,000 feet a difference of 12 per cent between dry and moist air, and at 12,000 feet the difference is only 1 9 per cent and the curves are rapidly approaching each other (see figure 3).

The following readings were taken on an automobile trip from Ann Arbor, Michigan up to Quebec, and back down through Vermont, New York, Pennsylvania, West Virginia, Tennessee, Oklahoma, and Texas. Readings were taken only on fairly cloudless days when it would be possible to get a fair estimate. A wait of three days was made in Oklahoma but it was too cloudy to get a fair reading, and as time was limited the journey had to be resumed without obtaining a reading.

A reading was taken in the Plains of Abraham, August 22, 1932.

9.00 a m	24 5%	10.20 a m	27 3%
9:30 a m	25 4%	10.40 a m	30 4%

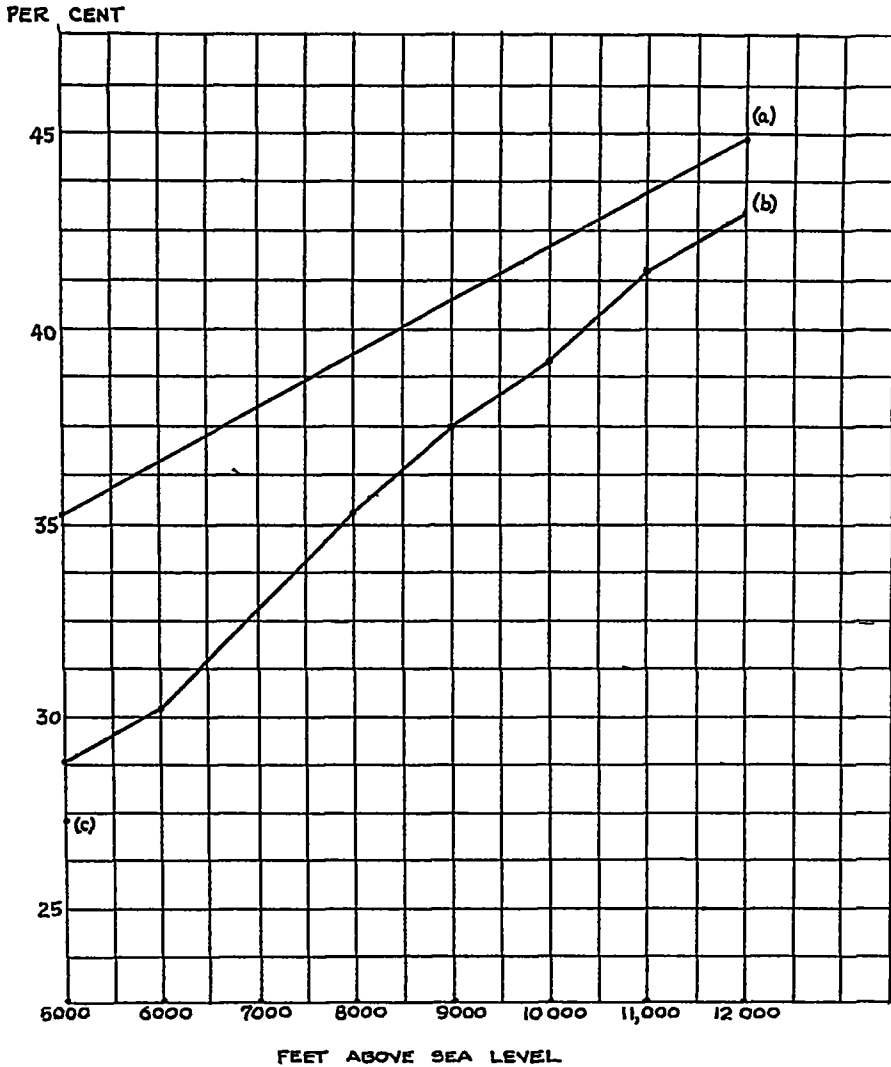


FIG 3 (a) Dry air (calculated) Rockwood's formulae, (b) moist air (calculated from vapor pressure at different altitudes), (c) direct determination

The results were 11 per cent lower than a reading at the Kiwanis Cabin on November 6

At Norton Mills on the Vermont-Quebec line

9 00 a m	23 6%	10 30 a m	33 0%
9 45 a m	27 5%	11 05 a m	36 3%
		12 00 noon	37 8%

The next clear weather was encountered at Romney, West Virginia, August 26, 1932 This reading shows the small percentages in the early morning

7 00 a m	0 9%	9 55 a m	21 9%
8 00 a m	7 7%	10 40 a m	25 4%
8 35 a m	13 2%	11 15 a m	26 7%
9 15 a m	17 4%	11 55 a m	27 0%

The next reading was taken on Vanderbilt Campus, Nashville, Tennessee August 29, 1932

7 45 a m 13 6%
8 35 a m 21 3%
9 15 a m 27 0%

10 20 a m 33 3%
12 15 p m 31 0%

PER CENT

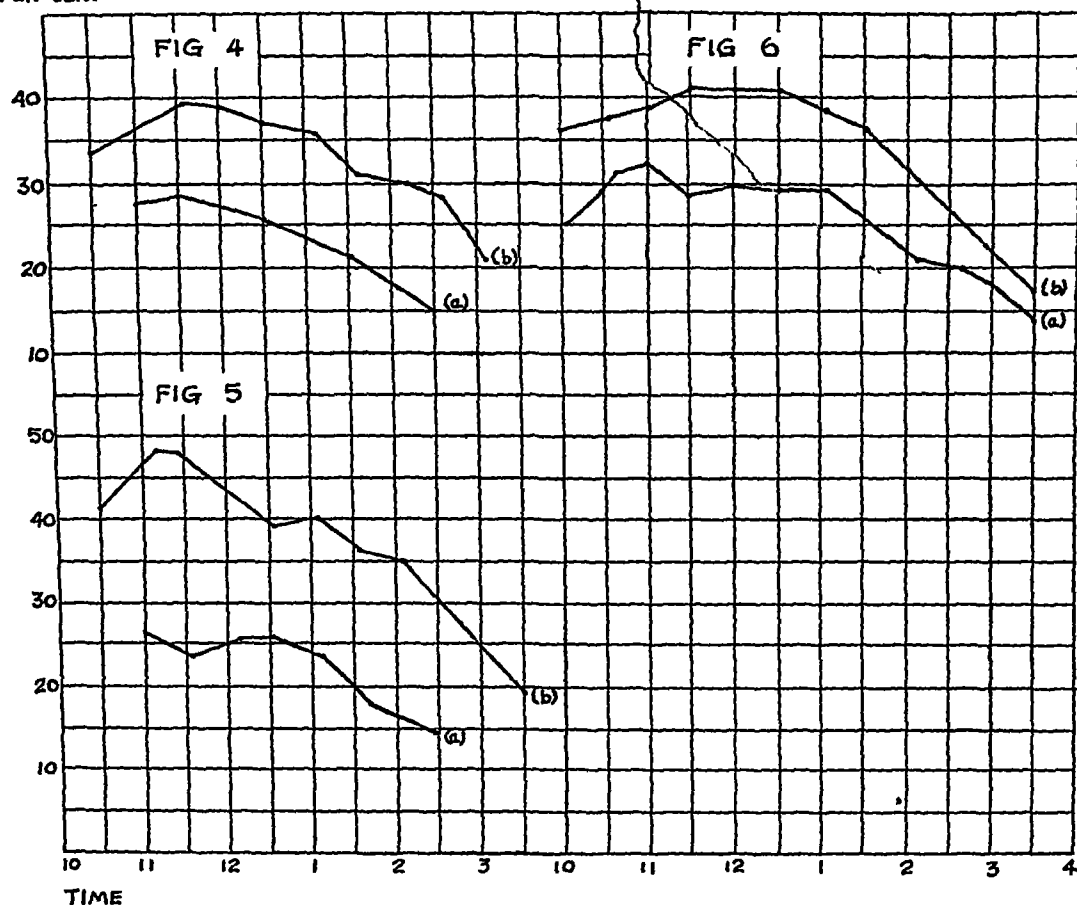


FIG 4 Observations Nov 14, 1931 (a) University Station, elevation 5,100 ft , (b) Carlito Springs, elevation 6,750 ft

FIG 5 Observations Nov 6, 1931 (a) University Station, elevation 5,100 ft , (b) Kiwanis Cabin, elevation 10,300 ft

FIG 6 Observations, average of several days (a) University Station, (b) Kiwanis Cabin

At Amarillo, Texas, September 3, 1932 the readings were

2 00 p m	44 0%	4 00 p m	12 3%
2 45 p m	32 2%	4 25 p m	7 4%
3 30 p m	21 3%		

Thus we see that as we get up onto the western plateau the readings are higher

Readings at Colorado Springs yielded about the same results as those at the University of New Mexico Station, and Pettit's readings at Mount

Wilson Observatory run about the same as our readings at the crest of the Sandia Mountains. This is perhaps more clearly shown by the charts (See figures 4, 5, and 6). We see that at Sunset View the readings are uniformly a little higher than those at the University, at Carlito Springs they go still higher, and at the crest the readings are consistently higher.

These findings harmonize with the findings of Hill, Frawley and Pettit, and while the study does not embrace enough locations over a sufficiently long period of time, the results point definitely to the conclusion that in high altitudes in arid and semi-arid regions, the percentage of short waves reaching the earth's surface is much higher than in low altitudes where the humidity is greater, and that density of population with its attendant increase of smoke and dust, also reduces the amount of health-giving rays received from the sun. The old idea that rickets was a condition which increased in proportion to the density of the population was in part true.

For ages it has been the practice of people in search of health, rest, relaxation and recuperation to seek the high, dry, arid and semi-arid regions, not knowing why they did so except that it was customary and that they felt a deep-rooted conviction that they were benefited by so doing.

We now find the scientific justification of this ancient practice. As in the case of many established practices that have been followed empirically for many generations, when we are able to get down to the facts we find ample scientific reason and explanation.

BIBLIOGRAPHY

- 1 BROUGHER, J. C. Viosterol (irradiated ergosterol) in treatment of parathyroid tetany, *Jr Am Med Assoc*, 1930, xciv, 471-473
- 2 SEEDS, L., and REED, C. I. Administration of viosterol in human parathyroid tetany, *Proc Soc Exper Biol and Med*, 1931, xxviii, 379-380
- 3 ROR, G. L'azione dell'ergosterina irradiata nella riparazione delle fratture, *Riforma med*, 1929, xlv, 1551-1552, abstract, *Jr Am Med Assoc*, 1930, xciv, 829
- 4 MORELLE, J. Influence des doses d'ergosterol irradié sur la consolidation du cal des fractures, *Compt rend Soc de biol*, 1931, cviii, 803-804
- 5 McCLENDON, S. J. Yeast and irradiated ergosterol in treatment of acrodynia, *Jr Am Med Assoc*, 1929, xciii, 455
- 6 MONASH, S. Viosterol in treatment of psoriasis, *New York State Jr Med*, 1931, xxxi, 889-890
- 7 BROWN, G. T. Treatment of urticaria and angioneurotic edema, *ANN INT MED*, 1929, iii, 591-603
- 8 JACOBSEN, C. Ekzemheilung durch Vigantol, *Deutsch med Wchnschr*, 1929, lv, 748-749, abstract, *Med Times and Long Island Med Jr*, 1930, lviii, 20
- 9 POTTENGER, F. M. Physiologic basis for employment of calcium in the treatment of asthmatic paroxysms, *Calif State Jr Med*, 1923, xxi, 293
- 10 BROWN, G. T. Perennial hay-fever, *Arch Otolaryng*, 1932, xv, 202-217
- 11 SPIES, T. D. Calcification of tubercles by means of irradiated ergosterol in experimental chronic tuberculosis, *Am Rev Tuberc*, 1931, xxiii, 169-174
- 12 LEVADITI, C., and LI, Y. P. Étude expérimentale de la calcification des lésions tuberculeuses sous l'influence de l'ergosterol irradié, *Presse med*, 1930, xxxviii, 1720-1725
- 13 MENSCHEL, H. Über eine Behandlungsmethode mit D-Vitamin (Vigantol) bei offener Lungentuberkulose. Eine pharmakologische Analyse am Krankenbett, *München med Wchnschr*, 1930, lxxvii, 239-242

- 14 HARTLEY Tetanoid syndrome in obstetrics, preliminary report, *Am Jr Obst and Gynec*, 1930, xix, 54-63
- 15 HARTLEY Tetanoid syndrome in pregnancy, report of case, *Minnesota Med*, 1930, xiii, 190-191
- 16 WIELAGE, M F *Status calcificatus*, Jr *Dental Research*, 1932, xii, 75-78
- 17 SANFORD, H N, GASTEYER, T H, and WYATT, L Substances involved in coagulation of blood of newborn, effect of ultra-violet radiation and Viosterol, *Am Jr Dis Child*, 1932, xliii, 566-568
- 18 SELYE, H Über die Blutgerinnungsbeschleunigende Wirkung des Vigantols, *Klin Wchnschr*, 1928, vii, 1891
- 19 MANVILLE, I A Ultra-violet component of sunlight of Portland, Oregon, measured by acetone-methylene blue method, *Am Jr Dis Child*, 1929, xxvii, 972-996
- 20 FRAWLEY, J M Ultra-violet light in California summer sunshine with special reference to its value in prophylaxis and treatment of rickets, *Am Jr Dis Child*, 1931, xli, 751-757
- 21 LARSEN, N P, and GODFREY, L S Ultra-violet in solar radiation, comparison at different localities near Pacific, Jr *Prev Med*, 1931, v, 25-36
- 22 ROCKWOOD, R S, and SAWYER, R A Ultra-violet transmission coefficient of earth's atmosphere, Jr *Optic Soc Am*, 1932, 513-524

THE INCIDENCE OF HYPERTENSION AMONG URBAN JAPANESE *

By HIROTOSHI HASHIMOTO, KEIJI AKATSUKA, ICHIRO TSUJII,
and HAJIME SHIRAISHI, *Tokyo, Japan*

CADBURY,¹ Cruickshank,³ Kilborn,¹² and others have called attention to the fact that the average blood pressure of the Chinese is lower than the average of Occidentals, the difference being about 10 mm of mercury Foster⁶ found, in his experience, that hypertension is rare in the Chinese. He found about 20 patients whose systolic blood pressures were more than 160 mm, among about 4000 patients examined on the medical service of the Hunan-Yale Hospital. Harris⁹ was of a similar opinion concerning the incidence of hypertension in Chinese. Foster⁶ and Tung¹⁸ reported that the blood pressures of Occidentals, mostly Americans, living in China, were about the same as those of the local Chinese, and that the blood pressure of the majority of these persons was lower in China than it was in America. Harris, however, did not find that the blood pressures of Europeans and Americans living in China, were lower than they would have been expected to be if the subjects had continued to live in Europe or America.

Musgrave and Sison¹³ found the blood pressures of Filipinos to be lower than the average given for Americans and Europeans living in their own countries, and also they found that the blood pressures of Americans apparently were lowered following long-continued residence in the Philippines. On the contrary, Chamberlain² reported that the blood pressures of Americans residing in the Philippines differed but little, if any, from the average in the United States, and that the average pressure of Filipinos was practically identical to that of Americans.

Although the reports from the Philippines concerning the blood pressures of Filipinos, and of Americans residing there, are conflicting, most of the investigators in China agree that the average blood pressure of the Chinese is lower than the average of Occidentals living in their own countries, and that hypertension is rare among the Chinese. The causative factors of such relatively low blood pressures among the Chinese, however, remain open to discussion. Various causes have been suggested: racial predisposition, a climate which lowers vasomotor tone, simplicity of life in China, absence of nervous strain, and so forth. If the blood pressures of Occidentals become lower following prolonged sojourn in China, as has been reported by Foster and Tung, the climate of China, or the simplicity of life there, may be responsible. If such a change in blood pressure does not occur during the sojourn of Occidentals in China, and if hypertension

* Submitted for publication June 26, 1933

From the St. Luke's International Hospital, Tokyo, Japan

among them is as common when they live in China as when they live in Western countries, as has been found by Harris, the hypotension of the Chinese may be regarded as due to such factors as constitution of the Chinese, their mode of life, or their diet

For those who have an interest in racial blood pressure and in the etiology of hypertension in general, it might be desirable to present data on the average blood pressure of the Japanese, and on the frequency of hypertension in Japan Ishioka,¹⁰ chief medical director of the First Mutual Life Insurance Company, Tokyo, Japan, after a study of the records of accepted risks, has stated that the average systolic blood pressure of healthy Japanese adults is slightly lower, and the average diastolic pressure decidedly lower, than that of Americans of corresponding age Table 1 shows the

TABLE I

Average Blood Pressures in mm of Mercury of Healthy Japanese Men, Resident in Japan and of Healthy American Men, Resident in the United States of America

Age, years	Japanese (Ishioka ¹⁰)		Americans (Symonds ¹⁷)	
	Systolic	Diastolic	Systolic	Diastolic
15 to 19	112.7	67.9	123.5	79.5
20 to 24	121.0	72.3	124.2	80.5
25 to 29	120.7	73.5	124.5	81.5
30 to 34	122.4	74.5	125.1	82.3
35 to 39	123.5	76.0	125.3	83.3
40 to 44	126.1	76.5	126.4	84.0
45 to 49	127.3	77.1	128.2	84.7
50 to 54	133.9	80.9	130.2	85.9
55 to 59	—	—	133.5	86.8

(The diastolic pressure was taken at the end of the fourth phase by Ishioka¹⁰ as well as by Symonds¹⁷)

average blood pressures of healthy Japanese males of various ages resident in Japan, as reported by Ishioka, compared with the average blood pressures of healthy American males (of all builds), resident in the United States of America, as published by Symonds¹⁷ As regards the incidence of hypertension among the Japanese, Norris¹⁴ stated, according to Volhard "The Japanese are rarely the subjects of arterial hypertension, a fact which suggests that diet and mode of life may account for this relative immunity" It has been common experience among physicians in Japan, however, to find hypertension fairly frequently among the Japanese, ever since portable sphygmomanometers have been extensively used Such information as that of Volhard, and of others, might have been derived from clinical experiences at a time when handy instruments for estimating blood pressure were not so extensively used as at the present, or from unsatisfactory statistical data Little information on this point has been found in the medical literature of Japan

We have derived the data about to be presented here from the records of the out-patient department of St Luke's International Hospital, Tokyo,

Japan From 1926 to 1932, we determined the blood pressures of 16,393 Japanese In the first two years, 1926 and 1927, we determined the blood pressures of all new patients examined in the medical social service section of the out-patient department In the last five years, 1928 to 1932, all new patients, including all pay patients, were examined Out-patients in the social service section were all poor, the majority of them were poorly paid wage-earners, and their standard of living was decidedly lower than that of patients who could pay ordinary rates for medical examination and treatment The average income of the out-patients in the medical social service section was as low as 684 yen a year for a family of five, whereas 977 yen a year is the minimal amount needed for support of a family of this size in the part of the city from which our poor patients come This has been shown in the estimates made by one of the social workers in our hospital

The blood pressures of all patients were taken after they had rested supine for about 10 minutes The sphygmomanometers used were Baumannometers (mercury) or Tycos instruments (aneroid), the latter were tested frequently against a standard mercury manometer to assure that they were accurate The auscultatory method was adopted, while the tactile method was used to verify the systolic pressure The diastolic pressure was taken at the beginning of the fourth phase, when the clear sound became muffled

The diagnosis of hypertension was made if a patient persistently had a systolic pressure of more than 160 mm of mercury, or if a patient had a diastolic pressure of more than 100 mm even though the systolic pressure was only moderately elevated There were 1,306 cases of hypertension among 16,393 out-patients thus examined, or 8.0 per cent Stated otherwise, 491 of 6,066 men (8.1 per cent) and 815 of 10,327 women (7.9 per cent) had hypertension

Of 10,058 poor patients, 943 (9.4 per cent) had hypertension 325 of 3,530 men (9.2 per cent), and 618 of 6,528 women (9.5 per cent) There were 363 cases of hypertension among 6,335 pay patients (5.7 per cent) 166 of 2,536 men (6.5 per cent), and 197 of 3,799 women (5.2 per cent) The incidence of hypertension among poor patients was considerably higher than among pay patients

Tables 2 and 3 show the incidence of hypertension by half decades of life among, respectively, poor patients and pay patients Among poor patients, hypertension occurred in a frequency of more than 10 per cent, at as early an age period as 36 to 40 years, whereas among pay patients a percentage of more than 10 per cent was found only after the age of 45 years At later age periods than those just mentioned, the incidence of hypertension for men and for women of both groups gradually and progressively rose To summarize, the incidence of hypertension was relatively low in early adult life, and higher in late adult life, and it was higher among poor patients than among pay patients The incidence among poor patients began to rise at an earlier age than it did among pay patients

TABLE II

Incidence of Hypertension Among Poor Out-Patients, St Luke's International Hospital, Tokyo, Japan (1926-1932)

Age, years	Patients examined				Hypertension Per cent	
	Patients with hypertension		All out-patients		Men	Women
	Men	Women	Men	Women		
13 to 15	1	1	215	235	0.5	0.4
16 to 20	13	10	606	713	2.1	1.4
21 to 25	18	61	637	1642	2.8	3.7
26 to 30	18	82	505	1350	3.6	6.1
31 to 35	10	75	355	847	2.8	8.9
36 to 40	34	64	290	532	11.7	12.3
41 to 45	32	54	229	338	14.0	16.0
46 to 50	40	49	212	294	18.9	16.7
51 to 55	48	67	180	229	26.6	29.2
56 to 60	37	47	113	136	32.7	34.6
61 to 65	39	49	102	107	38.2	45.8
66 to 70	21	26	55	59	38.2	44.1
71 to 80	14	33	31	46	45.2	71.8
13 to 80	325	618	3530	6528	9.2	9.5

TABLE III

Incidence of Hypertension Among Pay Out-Patients, St Luke's International Hospital, Tokyo Japan (1928-1932)

Age, years	Patients examined				Hypertension Per cent	
	Patients with hypertension		All out-patients		Men	Women
	Men	Women	Men	Women		
13 to 15	0	0	46	63	0	0.0
16 to 20	4	0	396	416	1.0	0.0
21 to 25	8	13	432	903	1.9	1.4
26 to 30	9	11	390	712	2.3	1.5
31 to 35	11	20	336	619	3.3	3.2
36 to 40	6	26	214	368	2.8	7.1
41 to 45	10	21	189	245	5.3	8.6
46 to 50	21	32	170	192	12.4	16.7
51 to 55	39	24	154	123	25.3	19.5
56 to 60	13	17	76	70	17.1	24.3
61 to 65	26	18	69	51	37.7	35.3
66 to 70	11	7	36	21	30.6	33.3
71 to 80	8	8	28	16	28.6	50.0
13 to 80	166	197	2536	3799	6.5	5.2

In the examination of the patients with hypertension, the attempt was made to obtain some information on matters which have been supposed to concern the etiology of hypertension. The family histories of patients with hypertension have been studied to determine whether there was any hereditary predisposition to hypertensive cardiovascular diseases. So far as the patients have informed us, cerebral apoplexy occurred in 21 per cent of the patients, hemiplegia in 2.5 per cent, and sudden cardiac death in 4.8 per cent.

The diet of the Japanese consists mainly of rice, vegetables, and fish. The Government Food Committee reported that the average daily food of the Japanese consists of 85 per cent carbohydrate, 3 per cent fat, and 12 per cent proteins. Animal proteins, mainly those from fish, comprise not more than 15 per cent of the total amount of proteins. It was very difficult to learn what actually had been eaten by the patients, but there is little doubt that at least the poor patients, among whom the incidence of hypertension was comparatively high, ate very little meat for meat is fairly expensive. Only about 0.4 per cent claimed a preference for meat. About 32 per cent of patients with hypertension used alcoholic beverages, but only about 7.5 per cent drank to excess. About 45 per cent of the patients used tobacco, but only 1.5 per cent used it in excessive amounts.

The body weight of about 65 per cent of the patients with hypertension was within the normal range. Twenty-four per cent of the total number were rather thin, whereas only 10 per cent were obese.

It was not rare to find evidence of syphilis among patients with hypertension. Wassermann tests were made of the blood of 614 patients with hypertension, and 148 of them, or 24.2 per cent, were positive. However, of 3,263 Wassermann tests of patients without hypertension, who were in the hospital, 821 (25.1 per cent) were positive, which compares fairly closely with the incidence among patients with hypertension. Of 1,635 women admitted to the maternity ward of the hospital, 172 (10.5 per cent) gave serologic evidence of syphilis. The majority of these women were from the same class of people as those who live in the district of the city from which the poor patients with hypertension came. This 10.5 per cent may indicate the incidence of syphilis among healthy women of this class, but may not be adopted as a control in our study of patients with hypertension, because a higher incidence of syphilis is usually found among patients than among apparently healthy people.

Urinalysis made in 746 cases of hypertension, in recent years, revealed nephritis in 163 (21.9 per cent). Albumin, erythrocytes and casts, were found in the examination of the urine of 19.7 per cent of poor male patients and of 25 per cent of poor female patients, and also, in the examination of the urine of 23.2 per cent of male pay patients and 14.6 per cent of female pay patients. About 78 per cent of our patients with hypertension were free from any clinical evidence of inflammatory disease of the kidneys. Of our patients with hypertension, 22.3 per cent had nocturia. Blood chemical studies of the majority of the patients with hypertension gave negative results. The non-protein-nitrogen of the blood of some of the patients examined was increased at the terminal stage of the disease.

The fate of the patients with hypertension was studied by repeated observation in the out-patient department or by continued observation in the ward. When they failed to return to the clinic, visiting nurses were sent to follow them up. In 1926 and 1927 repeated determinations were made of the blood pressures of 70 men and 119 women with hypertension. In

the course of medical treatment, mainly simple administration of bromides, there was slight, gradual subsidence, to a little less than 160 mm in the blood pressure of a number of these patients. Of the 70 men, 22.7 per cent, and of the 119 women, 11 per cent, died in the course of the period of observation. The male patients were observed for an average of 268 days, and the female patients for an average of 311 days. The highest mortality rate was in the age period 50 to 60 years. The mortality rate was 8.1 per cent among patients whose systolic blood pressure ranged from 160 mm to 180 mm, 14.8 per cent among those whose systolic blood pressure ranged from 180 mm to 200 mm, and as high as 26.2 per cent among those whose systolic blood pressure was continuously higher than 200 mm. The immediate cause of death was considered to be cerebral hemorrhage in 25.8 per cent of the cases from which the foregoing figures were derived, cardiac failure in 29 per cent, and uremia in 22.6 per cent. Other intercurrent diseases were the causes of death in 9.7 per cent. In the remaining cases no information was secured on this point. In 1928 and 1929, repeated determinations of blood pressure could be made of only 18 males and 51 females. The hypertension of 16.7 per cent of the men and of 27.5 per cent of the women gradually subsided. Of 393 patients who were diagnosed as hypertension during these two years, 132 were followed for a considerable time, the average was 347 days for male patients and 413 days for female patients. The visiting nurses reported that 11 of 45 men and four of 87 women had

COMMENT

It is very difficult to compare the incidence of hypertension in one country with that in any other country, because few data are available that show directly the incidence of hypertension in the population at large. The reports of life insurance companies concerning the results of medical examinations of applicants may show the incidence of hypertension among people who are presumably in good health, unconscious of physical impairment, for most of those with known cardiovascular or renal diseases do not apply for life insurance. Some people of the latter group will present themselves to hospitals or to medical practitioners if they become ill. But it must be remembered that many persons are not interested in life insurance, and many others who are actually ill are not conscious of physical impairment, among the latter are patients with hypertension of insidious onset. If data from the above-mentioned two sources are combined, however, some impression may be gained of the incidence of hypertension in the community.

Ishioke,¹⁰ of the First Mutual Life Insurance Company, Tokyo, reported that 60 cases of hypertension were discovered in the medical examination of 4,537 Japanese applicants for life insurance, an incidence of 1.32 per cent. He considered that hypertension existed, if the systolic blood pressure was consistently more than 15 mm above the average for persons of given age and sex. Among the persons with hypertension identi-

fied on this basis, average blood pressures within the various age groups varied from 153 to 189 mm, mostly more than 160 mm. As to the distribution by age of all applicants examined, 83.6 per cent were less than 40 years of age, and 16.4 per cent more than 40 years of age. The figures of Ishioka, just given, may be comparable with those of Frost⁷ in America. Frost studied the records of the medical department of the New England Mutual Life Insurance Company, and reported that among 146,992 Americans examined over a period of six years, 1919 to 1924, there were 2,568 cases of hypertension, an incidence of 1.74 per cent. Any person whose systolic pressure persistently was more than 15 mm above the appropriate average pressure, and whose diastolic pressure was more than 10 mm above the appropriate average pressure, was considered by him to have hypertension. Of all applicants examined, 76 per cent were aged less than 40 years and 24 per cent more than 40 years. The incidence of 1.32 per cent among Japanese is a little lower than that of 1.74 among Americans. From this comparison only, however, it can hardly be concluded that the incidence of hypertension among Japanese is lower than that among Americans, if it is taken into consideration that the comparison is between the results of two investigations carried out on materials of different age distribution.

Concerning the incidence of hypertension among patients in hospital, there has been little information in the medical literature of Japan. K. Yasui and S. Mori,¹⁰ having determined the blood pressures of all patients admitted to the Kyoundo Hospital, Tokyo, during four years, 1925 to 1928, found that of 7,365 patients, the systolic blood pressures of 2,689 (36.5 per cent) were more than 140 mm and of 1,218 of these more than 180 mm. Of all patients with hypertension, 43 per cent had nephritis. These data may be compared with those which have been reported by Gelman,⁸ and by Saller¹⁶ from Europe. Gelman, who had examined 3,761 patients in the Obuch Institute for Occupational Diseases at Moscow, reported that there were 344 whose systolic blood pressures were more than 140 mm, an incidence of 9.1 per cent. Saller found systolic blood pressures of more than 143 mm in 685 of 4,128 cases (16.6 per cent) at the Universitäts-Klinik of Kiel. The incidence of hypertension in the patients of one of the hospitals in Tokyo, differs markedly from that in the European hospitals named. Even when cases of nephritis with hypertension have been excluded, the number of cases of hypertension in the Japanese hospital would amount to 19.3 per cent. Such a high incidence may partly be attributed to the fact that the cardiovascular clinic of this hospital is well known among people of the city, and attracts more patients with hypertension than other hospitals attract.

Janeway,¹¹ in his study of hypertensive cardiovascular disease in Americans, found that 870 of 7,872 adult patients more than 20 years of age (11.1 per cent), at some time had systolic blood pressures of 165 mm or more. Of all patients examined by us, until the end of 1931, in the out-patient department of our hospital in Tokyo, 11,258 were aged more than

20 years Of 7,303 adults of poor families, 801 (11 per cent) had systolic pressures of more than 165 mm, and diastolic pressures of more than 100 mm Similar pressures were displayed by 241 of 3,955 pay patients (6.1 per cent)

Foster⁶ in his study of the incidence of hypertension in the Chinese, referred to the report of the Peter Bent Brigham Hospital, Boston, which showed that there were 236 cases of essential hypertension and 146 cases of chronic nephritis with hypertension among 4,940 patients on the medical service of the hospital in the two years, 1918 and 1919 The systolic blood pressures in these cases were more than 160 mm The incidence of hypertension among the patients included in the report quoted by Foster, then, was 7.7 per cent Among 16,393 Japanese examined in our hospital in Tokyo, 1,306 had hypertension, diagnosed by a standard similar to that used at Peter Bent Brigham Hospital, this gives an incidence of 8 per cent, which is fairly close to the rate of 7.7 per cent found in Boston

Riseman and Weiss¹⁵ stated that 2.9 per cent of male patients and 6.6 per cent of female patients admitted to the medical out-patient department of the Boston City Hospital in the 45 months from April 1925 to December 1928, had arterial hypertension The diagnosis of hypertension was made by them on 1,620 of 28,906 new patients examined. Of the patients with hypertension, the systolic pressure was more than 160 mm in 91.6 per cent, and less than 150 mm in 3.1 per cent The diastolic pressures were more than 100 mm in 66.1 per cent Of 1,620 patients with hypertension, 281 exhibited evidence of impaired renal and cardiac function, or of cerebral hemorrhage The incidence of hypertension of 2.9 per cent, for male patients in the Boston City Hospital, is considerably lower than our rate for male poor patients, 9.2 per cent, or our rate of 6.5 per cent for male pay patients, whereas the rate of 6.6 per cent for female patients in Boston falls between our two rates for hypertension among female Japanese in our hospital in Tokyo namely, lower than 9.5 per cent for poor women patients and higher than 5.2 per cent for pay women patients It is evident that hypertension is predominant in the later years of life Therefore, if a comparatively large number of elderly patients would happen to present themselves for examination in a certain hospital, there might be encountered a larger number of cases of hypertension than in other hospitals In the out-patient department of the Boston City Hospital, 54.3 per cent of the male patients, and 66.9 per cent of the female patients were aged less than 45 years In our hospital 79.7 per cent of all male patients and 86.9 per cent of all female patients examined in the out-patient department were less than 45 years of age

Although a diet high in protein used to be mentioned as one of the factors responsible for inducing the hypertensive cardiovascular disturbances, it is of interest to note that hypertension was not rare among our charity patients whose diet is low in protein

As one of the factors that influence the incidence of hypertension, racial

difference has been pointed out by some authors. However, of the mixture of Oriental races of which the Japanese people are composed, no race which is anthropologically different from the Chinese is predominant, yet hypertension is more frequently found among the Japanese than among the Chinese. Foster's finding at the Hunan-Yale Hospital has been mentioned earlier in this paper. As to climate, that of Tokyo differs not much from that of many cities in China. The diet of the Japanese, especially that of poor people, is rather lower in protein than that of the Chinese.

Fishberg⁵ noted that hypertension is not rare among negroes in New York City, while Donnison⁴ pointed out the fact that hypertension scarcely occurs among negroes living in a primitive state in Africa. Among the patients examined by us, hypertension was found to occur more frequently and at earlier periods of life among poor people than among those able to pay for medical attention. The majority of the charity patients are poorly paid wage-earners who are struggling for existence, their daily work involves much nervous and physical strain. Living in a thickly populated, factory district of the city, they are not at all protected against the various infections that may affect the kidneys or the cardiovascular system. If the incidence of hypertension among urban Japanese really differs from that among the Chinese, the difference should not be attributed to racial peculiarities but rather might be explained as being due to the different industrial environment and the different attitude of the people to it.

SUMMARY

Comparative studies of the incidence of hypertension among Japanese and among Americans or Europeans, based on statistical data derived from the reports of life insurance companies and from hospitals in Japan and in America or Europe, indicate that hypertension is by no means rare among urban Japanese, since it is found nearly as frequently as among Americans or Europeans. If the incidence of hypertension among urban Japanese is higher than among Chinese, the difference should not be explained as being due to racial peculiarities, but rather it might be attributed to the more intricately organized industrial life of Japan, and the reaction of the Japanese to the conditions such a life entails.

BIBLIOGRAPHY

- 1 CADBURY, W. W. Blood pressure of normal Cantonese students, *Arch. Int. Med.*, 1922, **XX**, 362-377, *China Med. Jr.*, 1923, **XXVII**, 823-833.
- 2 CHAMBERLAIN, W. P. A study of the systolic blood pressure and the pulse rate of healthy adult males in the Philippines, based on 6,847 blood pressure readings on 1,489 individuals and an equal number of pulse counts on the same persons, *Philippine Jr. Sci.*, 1911, **VI**, 467-482.
- 3 CRUICKSHANK, E. W. H. Physiological standards in north China: blood pressure studies, alveolar air gases, *China Med. Jr.*, 1923, (supp.) **XXVII**, 1-44.
- 4 DONNISON, C. P. Blood pressure in African native, its bearing upon etiology of hypertensia and arteriosclerosis, *Lancet*, 1929, **I**, 6-7.

- 5 FISHBERG, A M Hypertension and nephritis, 1930, Lea and Febiger, Philadelphia, p 428
- 6 FOSTER, J H Blood pressure of foreigners in China, Arch Int Med, 1927, xl, 38-45
- 7 FROST, H M Hypertension and longevity, Boston Med and Surg Jr, 1925, cxciii, 241-251
- 8 GELMAN, J Hypertoniestudien II Mitteilung Alters- und Berufsverschiebungen im hamodynamischen System, Ztschr f klin Med, 1927, cvi, 310-319—Hypertoniestudien, klinische Formen der Hypertonie, *ibid*, 320-336
- 9 HARRIS, E F Quoted by Foster
- 10 ISHIOKA, S Blood pressure of policy-holders, Hoken Igaku Zasshi, 1921, xx, 41
- 11 JANEWAY, T C A clinical study of hypertensive cardiovascular disease, Arch Int Med, 1913, xii, 755-798
- 12 KILBORN, L G Blood pressure of Szechwanese students, China Med Jr, 1926, xl, 1-7
- 13 MUSGRAVE, W E, and SISON, A G Blood pressure in the tropics, a preliminary report, Philippine Jr Sci, 1910, v, 325-329
- 14 NORRIS, G W Blood pressure, its clinical applications, 1917, Lea and Febiger, Philadelphia, p 279
- 15 RISEMAN, J E F, and WEISS, S Age and sex incidence of arterial hypertension, Am Heart Jr, 1929, v, 172-190
- 16 SALLER, K Über die Altersveränderungen des Blutdrucks, Ztschr f d ges exper Med, 1928, lviii, 683-709
- 17 SYMONDS, B The blood pressure of healthy men and women, Jr Am Med Assoc, 1923, lxxx, 232-236
- 18 TUNG, C L Relative hypotension of foreigners in China, Arch Int Med, 1927, xl, 153-158
- 19 YASUI, K, and MORI, S Nihon Naika Gakkai Zasshi, 1928, xvi, 122

GASTROINTESTINAL ALLERGY IN CHILDREN *

By HORTON CASPARIS, M D , F A C P , *Nashville, Tennessee*

THE PURPOSE of this discussion is to consider some of the gastrointestinal allergic manifestations in children and to suggest their relationship and similarity to certain symptoms which occur in adults and which are not generally considered as having an allergic basis. In this brief discussion no attempt will be made to consider extra-gastrointestinal allergic signs and symptoms, such as angioneurotic edema, urticaria, eczema, migraine, allergic rhinitis, asthma, and so forth, any one of which may result from the ingestion of food to which the individual is over sensitive, but, only evidences of local allergic irritation to the gastrointestinal tract will be taken up.

GASTRIC MANIFESTATIONS

Not infrequently one sees infants who begin to vomit as soon as they take food (breast milk). Others may take breast milk well and begin to vomit when cow's milk is begun. Still others do well on milk and begin to vomit only when other articles of food are added to their diet, such as eggs, orange juice, chocolate, nuts, and so forth. In other words, one may encounter allergic vomiting at any stage of childhood, depending upon when the exciting substance which is responsible for the symptom of vomiting becomes a part of the diet. I do not mean to give the impression that vomiting is a very common symptom of allergy, or that allergy figures very prominently as a cause when we consider all the vomiting that occurs in children. Just as allergy produces many symptoms other than vomiting, so vomiting has many causes other than allergy. The point is that when allergy is the cause of vomiting, the vomiting tends to be of a persistent nature and no relief is obtained unless the causative factor is recognized and removed completely or partially, or unless chance removes the cause for us, which not infrequently happens.

The earliest type of allergic vomiting which we see is that in small infants which begins when the infant first takes food, or soon after. In these infants hypertrophic stenosis of the pylorus is nearly always thought to be the cause of the vomiting. And of course, probably in the majority of instances of persistent vomiting at this period, it is the cause. However, I have seen a number of infants with early persistent vomiting whose condition had been diagnosed hypertrophic stenosis of the pylorus but whose symptoms were relieved only when it was found that they were sensitive to milk and when the cause of trouble was removed. I also know of five infants who were operated on in various hospitals for hypertrophic stenosis.

* Read at the Montreal Meeting of the American College of Physicians, February 7, 1933.

From The Department of Pediatrics, Vanderbilt University Medical School, Nashville, Tennessee

of the pylorus, but were found to have no hypertrophy. Later their symptoms were relieved when the allergic nature of the condition was discovered and the causative factor was removed.

A few months further up the scale of infancy we not infrequently encounter vomiting when new articles of food are added to the diet. This of course does not necessarily mean that the child is over sensitive to the new food unless the vomiting occurs each time the food is given, and even then, one looks for additional evidence to prove allergy as the cause. A family history of allergy in the mother, in the father, or in both is usually present when the infant presents this particular symptom of allergy. A positive skin test to an extract of the food is usually present. This, however, is not always so, just as in adults. Other allergic manifestations in the patient such as urticaria or eczema should be sought for, but such skin manifestations do not usually occur coincidentally with the gastrointestinal manifestations of allergy. In older children one may get a history of previous skin manifestations. Finally, strong supporting evidence of the true nature of the condition is obtained if there is a cessation of symptoms upon eliminating the suspected food from the diet, and if there is a recurrence of symptoms when the food is again added to the diet. Unfortunately the situation not infrequently is complicated by the fact that there is in the diet more than one food to which the child is sensitive.

It is usually later on in childhood that we meet the familiar condition called cyclic or recurrent vomiting. Attacks of cyclic or recurrent vomiting may not always be due to allergy but I have had occasion in the case of several children to prove their allergic basis. For example, one 10 year old girl had had a number of attacks of cyclic vomiting. She was found to be skin sensitive to milk. As long as milk and milk products were left out of the diet there was no trouble. Another child had attacks once a year when he went to the circus. The attacks were attributed to excitement and exhaustion, but on further questioning it was found that he ate peanuts only during his visit to the circus, and when tested to peanuts he was found to be sensitive. The parents doubted the validity of our suggestion that peanuts were probably responsible for his trouble and somewhat later gave him peanuts. A severe attack followed. By accident the experiment was repeated several times with the same results. There is further evidence and support of the allergic nature of cyclic vomiting in that a number of the adults who suffer with migraine give a history of cyclic vomiting during childhood. This of course presumes that migraine is an allergic manifestation.

INTESTINAL MANIFESTATIONS

Again, early in infancy, one sees children who do not vomit but who have severe intestinal symptoms, such as colic, frequent bowel movements containing mucus, and the passage of a great deal of gas by bowel. The frequent movements are not watery as in diarrhea, but are soft, are apt to be

small, and nearly always contain mucus. The colic mentioned here is genuine colic and not mere hunger pains which so frequently are called colic. This type of manifestation is similar to much of the mucous colitis of adults. In children, however, one seldom sees the spastic type of colitis. These children gain weight well and develop well if given an adequate amount of food but almost run the family crazy until relief from their pain is obtained by finding the cause of their trouble and removing it. As opposed to other children who may temporarily have similar symptoms due to other causes, these small infants are not ill but are merely very uncomfortable. The allergic nature of this condition is readily suspected if one has had previous experience with such infants, but proof of the diagnosis is to be obtained only by more or less the same methods as those indicated above in connection with vomiting. Symptoms like these may occur during any stage of childhood and even in adults. For example, a small child who had suffered for two months with the above mentioned symptoms was found to be sensitive to milk and was completely relieved when he was placed on a dried milk preparation which of course had been heated. Various fresh milk preparations had been tried with no benefit. The probable explanation of the relief which these children often get when placed on a milk preparation which has been subjected to prolonged heating is that there are two factors in milk to which they may become sensitive and one is apparently heat labile. This is the explanation recently offered by Lewis and Hayden¹. Another older child (12 years of age) passed a great deal of gas, had soft bowel movements containing much mucus, and had colicky pains in the abdomen. He was found to be sensitive to chocolate and on repeated occasions later his symptoms recurred following the ingestion of chocolate. Still another patient (an adult) who had complained of marked abdominal pain for three years, and for a year had had typical severe mucous colitis symptoms, was found to be sensitive to milk and on the removal of milk and all milk products from his diet all symptoms disappeared and his weight rapidly rose from 130 to 200 pounds. He was six feet two inches tall, very much under weight and had made milk and various milk drinks a constant part of his diet for the purpose of improving his physical condition. Probably because of the constant presence of milk in his diet he had become suspicious of the bad effects of almost everything he ate. None of these suspected foods caused any trouble after milk was eliminated. On two occasions later the unintentional addition of milk products (frozen custard and swiss cheese) to his diet resulted in the recurrence to a marked degree of his previous symptoms.

There is another group of individuals whose symptoms probably come from intestinal irritation, in whom abdominal discomfort is the chief complaint. Their symptoms in general are similar to those of the group described above except that the bowel movements as a rule are not frequent. Some indeed of these individuals are constipated. The members of this group are usually older children and adults. The symptoms in certain cases have been repeatedly produced by giving to the patients foods to which they

are sensitive In some instances there is dull pain, and in others sharp cramp-like pain For example, one boy who had had attacks of cyclic vomiting for several years began to have abdominal discomfort later which prevented his sleeping and caused him trouble during most of the day from time to time These latter symptoms had continued for three or four years when we first saw the boy and found him to be sensitive to chocolate and tomatoes These two articles of food were removed from his diet following which there was complete relief from discomfort and a gain of 10 pounds in weight during the next month While I have had no opportunity to prove the presence of spasm of the intestine in these cases, its occurrence is suggested by the fact that relief of symptoms sometimes results from the administration of atropine There is much reason also to believe that the enterospasm, which is sometimes the only finding when the abdomen is explored surgically for appendicitis or intestinal obstruction, is of this nature In some cases the severe pain followed some time later by vomiting might quite naturally suggest intestinal obstruction Relief has been obtained in just this type of patient from the administration of atropine I recognize the danger of assuming that symptoms like these have an allergic basis, and of course one should never make this assumption except as a last resort because of the great danger of missing other abdominal conditions with like symptoms which produce more serious consequences if the surgeon does not intervene However, repeated attacks of this type not localized to the appendix region, associated with eating of certain foods and occurring in a patient with a personal or family history of allergy, should always be suggestive of an allergic etiology In many instances the confirmation of positive skin tests may be obtained

TREATMENT

After one finds the food or foods which are responsible for the allergic symptoms, treatment consists of removing the offending foods from the diet, or of modifying the food so that it will not cause symptoms, or of modifying the patient's response to the food For example, if a patient is found to be sensitive to chocolate, it is not difficult to eliminate chocolate from the diet Elimination of the offending food, if this is possible, is the most simple method of treatment and produces the most clear-cut results However, if a small infant whose sole article of diet is milk is sensitive to that milk, then elimination is difficult In this case it has been found that cow's milk that has been subjected to varying degrees of heat, such as dried milks or evaporated milk, may be taken without producing symptoms, when fresh milk cannot be tolerated One of the factors in cow's milk to which children often become sensitive can be completely or partially destroyed by heat If this modification of milk does not result in relief of symptoms it then becomes necessary, if the symptoms are severe enough, to change to some other food, such as goat milk or in some instances to soy bean preparations

In older children where there is sensitiveness to several foods, and elimi-

nation would unduly restrict the diet, the patient's response to these foods usually can be modified through a process of what one may call desensitization. Patients themselves have a tendency to carry out this desensitization through repeatedly taking the foods to which they are sensitive, provided they do not take enough to produce severe symptoms. This is what the layman calls "out-growing" the condition. Desensitization to a food can be carried out through starting the patient on infinitesimally small amounts of the food by mouth and gradually increasing the amount. One must go slowly enough to avoid the production of symptoms if possible. This requires a great deal of patience, but we have successfully desensitized a number of infants to egg in this manner. The same principle is used in a more rapid desensitization to one or more foods by subcutaneous injections, beginning with very weak dilutions of extracts of the foods and gradually increasing the amount. One should begin with an amount sufficiently small so as to be sure that no demonstrable reaction occurs. We often begin with as weak a dilution as 1-1,000,000, or even less if the sensitiveness is severe. In this way we have successfully desensitized a number of children to foods to which they are sensitive, or at least have made it possible for them to take these foods without any discomfort—foods, the ingestion of which previously produced severe symptoms.

The above methods not infrequently are attended by discouraging results. Failures in many instances may be due to lack of patience, or may be explained by the fact that treatment has not included all of the foods which are contributing to the symptoms.

I am well aware of the fact that all of this is quite familiar to those working especially in the field of allergy, but the discussion seemed justified because of the fact that we continue to see large numbers of patients belonging to this group whose symptoms have received abundant unsuccessful treatment without any thought having been given to allergy as the probable etiologic factor.

BIBLIOGRAPHY

- 1 LEWIS, J. H., and HAYDEN, H. C. Effect of heat on antigenic properties of milk, *Am Jr Dis Child*, 1932, xlv, 1211-1220.

ABSCCESS OF THE AORTA *

A CASE WITH PERFORATION WITHOUT ANEURYSM

BY CHARLES W. MILLS, M.D., F.A.C.P., and MAX PINNER, M.D.,
F.A.C.P., *Tucson, Arizona*

PURULENT lesions of the aorta are not frequent. Oetiker¹⁰ in 1924 found 81 cases in the literature to which she added five observed in Askanazy's institute. Auerbach¹ in a recent publication brought the cases up to a total of 133, this does not include cases of carcinomatous or tuberculous origin. According to the latter author, in 42 of these cases rupture of the aorta occurred, but in only 12 cases did this happen without the preceding formation of an aneurysm. Aneurysm occurred at the site of the lesion in a total of 56 cases. The case to be presented here would have to be added to the small group of 12 cases in which a pyogenic lesion of the aorta caused rupture without the formation of a localized dilatation.

These 12 cases were reported by 10 authors all of whose reports appeared between 1901 and 1931. They are, in chronological order: Kahlden,¹⁰ Witte,³¹ Scheuer,²¹ Cooper,⁴ Luzzato,¹⁴ Schlagenhauser,²⁵ (3 cases), Hanser,⁸ Stubler,²⁹ Desclin,⁵ and Levinson.¹² Pyogenic lesions of the aortic wall have been known for a long time.† The oldest detailed description must apparently be credited to Spengler,²⁸ who found, in a man 38 years of age, a small abscess in the media, just above the valve; this patient had died of a pyemia following tonsillitis.

An infectious process in the aortic wall may obviously enter from the lumen, through the vasa vasorum, or by direct contact from neighboring tissues. A frequent mechanism of origin is that by direct contact from infectious lesions in the aortic valves. Nauwerck and Eynich¹⁸ drew attention to the existence of a primary verrucous aortitis, that is, one which occurs in the absence of valvular lesions. In a considerable number of the cases reported in the literature, the mode of entrance into the aorta is not mentioned or could not be reconstructed. Auerbach, who is the last to have made a careful analysis of the available cases, concludes that in the 41 cases in which pertinent data are at hand, the infection entered through the intima in 15, through the vasa vasorum in 14 and from adjoining tissue in 12. Oetiker ascribes 25 cases to contact from adjoining tissue, 12 to direct contact, and 47 to hematogenous metastasis—13 of these latter through emboli in the vasa vasorum and 34 through infection from the lumen. In the last

* Received for publication March 6, 1933.

From the Desert Sanatorium and Institute for Research, Tucson, Arizona.

† According to Spengler (1852), Rokitsky quotes an observation by Andral who described a case with about half a dozen hazel-nut sized abscesses below the intima of the aorta, but Rokitsky—still according to Spengler—doubted the correctness of Andral's observation. In 1856 Rokitsky²¹ discusses (without the above reference to Andral) purulent arteritis leading to aneurysm and terminating in rupture or pyemia.

34 reported cases, the infectious focus was superimposed in 22 cases on other aortic lesions, such as arteriosclerosis, lipiodosis of the intima, aortitis fibrosa or stenosis. In only three of these cases was the aorta reported to be normal with the exception of the purulent foci, in nine cases no mention was made of the condition of the aorta. Saphir and Cooper,²³ and Hausbrandt⁹ have reported cases in which pyogenic foci were superimposed on syphilitic aortitis.

The primary portal of entry is demonstrable in a minority of cases. This is obviously due to the fact that the primary focus may have healed completely long before the aortic lesion manifests itself, furthermore the primary focus may be rather insignificant in size and its site be difficult of detection. Purulent foci of many kinds may be the primary source of aortic infection, the following have been cited: tonsillitis (Spengler, Hausbrandt), traumatic phlegmonous foci (Scheuer, Koritschoner,¹¹ Edenhuizen,⁶) inguinal bubo (Foà⁷), rheumatic disease (Kahlden, Witte, McCrae¹⁶), endocarditis (Auerbach), salpingitis (Schmorl²⁶), mediastinal abscess (Roesner,²² Oliver,²⁰ Desclin), sepsis lenta (Siegmond²⁷), furunculosis (Buchaly³), pericarditis (Stubler, Maresch¹⁵), gonorrhea (Lindau¹³), chronic cystitis (Stumpf,³⁰ Auerbach), puerperal sepsis (Hanser), scarlet fever (Awdejeff²), vertebral caries (Schlagenhauser), erysipelas (Schlagenhauser), pulmonary infection (Luzzato). This list is incomplete and is included only in order to give an idea of the unlimited variety of lesions that may be the cause of purulent changes in the aorta.

A similar variety exists in regard to the offending microorganisms. According to Auerbach, microorganisms have been found in 70 cases, they were most frequently streptococci (in 26 cases), pneumococci (in 12), staphylococci (in 8), gonococci (in 2), "micrococci" (in 2), influenza bacilli (in 1) and anthrax bacilli (diagnosed on morphological grounds only (Oliver)) (in 1). Edenhuizen and v Zalka³² and others have reported tuberculous lesions of the aorta.

In 99 cases the localization of the process is mentioned, as follows: ascending portion of the aorta, 70, arch, five, descending thoracic, eight, abdominal, 13, multiple localization in three.

In the 12 cases of purulent aortitis in which rupture occurred without aneurysm, the localization of the lesions was as follows: ascending portion, five (Scheuer, Kahlden, Stubler, Luzzato, Levinson), descending portion, four (Hanser, Witte, Desclin, Cooper), abdominal portion, three (Schlagenhauser). Perforation occurred into the pleural cavity in three cases (Scheuer, Luzzato, Cooper), into the lung in one (Hanser), into the pericardium in four (Kahlden, Stubler, Luzzato, Cooper), into the retroperitoneal space in three (Schlagenhauser), into the bronchial tree, that is the left main bronchus, in one (Witte). In Desclin's case the rupture occurred into an abscess between the aorta and pulmonary artery so that no bleeding took place. Pathological data throwing light on the probable mode of spread of the infection in these 12 cases may be outlined as follows:

Tonsillitis the probable primary focus (Levinson)	1 case
Phlegmonous inflammation of left foot, pulmonary infarction, involvement of aortic intima (Scheuer)	1 case
Puerperal infection from a recto-vaginal fistula, embolic pulmonary abscess, involvement of aortic intima (Hanser)	1 case
Rheumatic fever, fibrinous pericarditis, spread from pericardium into media of the aorta (Witte, Kahlden)	2 cases
Caries of lowest thoracic and first lumbar vertebrae, involvement of aortic intima (Schlagenhauser)	1 case
Erysipelas of left leg with probable embolism into aortic wall (Schlagenhauser)	1 case
Abscess in Douglas' space following a recent trauma, involvement of the aortic intima at the bifurcation (Schlagenhauser)	1 case
Pericarditis, hematogenous spread into the aorta (Stubler)	1 case
Abscess, origin unknown, between aorta and pulmonary artery, involvement of aorta (Desclin)	1 case
Chronic pulmonary infection with carnification, involvement of aortic wall (Luzzato)	1 case
Influenza one year before death, no purulent lesions found except ulcers in aortic wall (Cooper)	1 case

In all but Desclin's case, hemorrhage from the aorta was the cause of sudden death. In Desclin's case (Case V in his paper), the rupture of the aorta had occurred a considerable time before death. The immediate cause of death was massive hemopericardium in four cases (in one of these combined with hemothorax), massive hemorrhage into the retroperitoneal space in three, hemothorax alone in one, massive hemoptysis in two, and copious bleeding into the lung in one.

In practically all of these cases, clinical data are very scanty or lacking altogether. The symptomatology depends on the nature of the primary disease and on the localization of the aortic lesion. The impression is gained that localized pain may or may not be present, and that it is dependent not on the pyogenic lesion per se, but on effects of pressure and on associated pathological changes, such, for example, as pericarditis. Whenever symptoms, such as pain or dyspnea, are mentioned they may be adequately explained by associated lesions. Cooper mentions in his case severe pain in the left hypochondrium and the upper dorsal region, and delayed passage of food through the esophagus. In cases with aneurysm, pain is much more frequently mentioned.

In a number of the papers quoted above, detailed descriptions are presented of the histological changes in purulent aortitis. In general, they are essentially the same changes as in purulent inflammation in other tissues. Both Levinson and Auerbach emphasize the necrotizing processes in the media, that is particularly in the elastic elements. These two authors and Desclin point out that the exudate cells in the adventitia are predominantly polymorphonuclear cells, while those in media and intima are chiefly mononuclear. Certain structural details of the lesions provide the criteria for a reconstruction of the pathway of the infectious process.

CASE REPORT

G. H. C., a University professor, 59 years old, came to the office on April 10, 1931, complaining of a severe cold, with chills, fever, cough and pain in the chest. His father, an exceptionally healthy man, had died at the age of 90. His mother

died at 68 of apoplexy. A brother and a sister had diabetes, and a paternal aunt and a sister had died of carcinoma.

The patient had a severe attack of "croup" when one year old, and subsequently up to the age of 42 several attacks of sore throat which he thought were diphtheria although he was never treated with antitoxin. He had an attack of jaundice at seven, whooping cough at eight, measles at 22, and mumps at 25. Five years before, when 54, all his teeth were extracted on account of pyorrhea.

He had led a very healthy life, denied venereal disease, and had never used alcohol or narcotic drugs. He had smoked moderately until two years before. He had never married. For the past 20 years, working at his profession of teaching, he had never missed any time from work on account of illness.

When 28 he had an attack of "grippe." Two years before, when 57, he had an attack of "influenza" with severe cough and hoarseness. He did not know whether he had fever, but worked throughout the attack which lasted about a week. During this illness he also had conjunctivitis which was epidemic at the time.

Since then, he had a few acute head colds and a tendency to stuffiness and scabby secretions in his nose. He had no headaches. Also, since this attack he had a few chest colds, always with much cough but with difficulty in raising any sputum. He did not have chronic cough, hemoptysis or asthma.

For the past few months he had noticed polydipsia and accompanying polyuria.

About ten days before he developed a head cold followed by cough and probably fever. He had felt badly, not eaten well, and had one vomiting attack a week before. Two days before, feeling feverish, he treated this by getting into a tub of cold water. Since then he had pain of a pleuritic character in the left chest, felt more feverish, and his cough was tighter.

The following notes were made on the physical examination at the first visit, and on the laboratory findings and roentgen-ray films a few days later.

PHYSICAL EXAMINATION Wt 161 Pulse 92 Temp 101.4 B P 130-88 Tired appearing, elderly man, well nourished. Lips slightly cyanotic.

Eyes Sclerae slightly icteroid. Pupils equal and regular, react sluggishly to light.

Upper respiratory tract No tenderness over frontal sinuses or antra. Mucous membrane of nose is very dry and in left nostril there is a mass of bloody scabs. Pharynx, pillars and posterior palate show a bright red injection. Right ear drum normal, left a little injected in the upper half.

Mouth The teeth all absent. Tongue covered with brownish coat.

Lymph-nodes Not enlarged.

Thyroid Not enlarged.

Chest Well formed. Expansion fair, and apparently equal.

Heart Apex beat in fifth intercostal space inside mid-clavicular line. Percussion outline not enlarged. Sounds normal.

Lungs Percussion note good. Breath sounds rather harsh throughout. At the right base posteriorly a few medium râles are heard, not changed by cough. Fluoroscopy of chest. Heart is of broad shape. Mediastinal shadow broad. Posterior space clear. Diaphragm appears normal. No definite abnormalities in lung fields.

Abdomen Full. No rigidity, tenderness or masses. Liver and spleen not felt. Left inguinal ring is large and on coughing a small hernia is felt.

External genitalia Normal.

Extremities Joints clear. Fingers not clubbed.

Reflexes Knee jerks obtained with difficulty, only after reinforcement. Romberg negative.

LABORATORY FINDINGS 4-13-31

Urine Voided specimen Acid SG 1025 Albumin ++ Sugar 2 per cent
 Acetone positive Indican trace Bile negative Microscopical very
 rare white blood cells, no red blood cells, 4 hyaline and 6 finely granular casts
 per low power field

Blood Red blood cells 4,900,000, hemoglobin 90, white blood cells 23,000 Dif-
 ferential polymorphonuclears 94 per cent, small lymphocytes 2 per cent,
 large lymphocytes 2 per cent transitional 2 per cent

Blood sugar 156 mg

Non-protein-nitrogen 27.6 mg

Wassermann Negative

Sputum 30 c c, mucoid, blood streaked, no tubercle bacilli, many streptococci,
 staphylococci and pneumococci

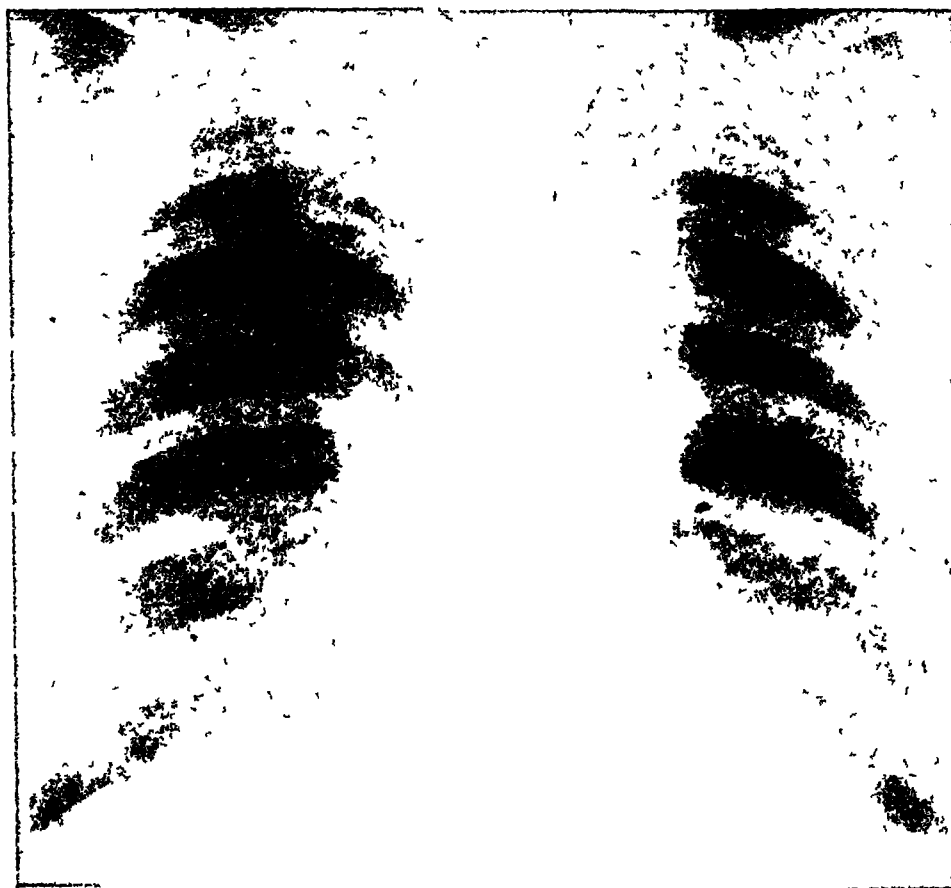


FIG 1 Roentgenogram of 4-13-31, showing the shadow adjoining the left upper mediastinum (Details in the text)

ROENTGENOLOGICAL FINDINGS

Sinuses P. A. (4-13-31) There is a little erosion of the upper walls of the frontals, suggesting an old frontal infection. The antra are clear. The septum is deflected a little to the right.

Chest (4-13-31) There is a marked density in the upper left mediastinum extending from about the fourth rib posteriorly down to the eighth, with its lateral margin 7.0 cm from the midline. The lateral margin is fuzzy in outline. Through the density there is a moderate amount of honey-combing. The pleura around the left lung is thickened. The bony thorax is normal. There is a little thickening of the pleura on the right. (See figure 1)

Chest (Bedside 4-21-31) No appreciable change since the previous film was taken

Lateral chest (4-24-31) The lung fields are not clear because of motion. The thickened pleura can be traced along the anterior wall. There is very marked bridging between five of the lower thoracic vertebrae

The patient was put to bed at his home. On the morning of the second day following he had a chill and a rise of temperature. He was seen in the afternoon at home, at which time he had a tight cough, pain in the left chest near the sternum, a temperature of 103°, pulse 92, and respirations 36. There was an impairment of resonance, harsh breathing and moist râles at the right base posteriorly, but no abnormal signs were found in the left chest. He was thought to have a pneumonia at the right base and was sent to a hospital.

He was put on strict bed rest, and, as soon as the glycosuria and acetone were reported by the laboratory, a restricted carbohydrate and low fat diet with insulin was ordered. He had no medication except tincture of digitalis, 60 minims a day, for about a week.

During his first week in the hospital the respiratory symptoms improved and the glycosuria and acidosis disappeared. His maximum daily temperature became 100.2°, his pulse 72, and respiration 30. Following this improvement, however, he had a sudden exacerbation with a pulse of 104 and respirations of 40, and on the next day a rise of temperature to 101.6°, but without other change in symptoms or chest signs.

On the tenth day after admission to the hospital he developed a conjunctivitis in the left and two days later in the right eye, which subsided after a few days.

On the twelfth day he passed a black tarry stool with a few streaks of bright blood, but had no accompanying nausea, vomiting, pain in the abdomen or other symptoms.

On the thirteenth day he began to have pain in the left shoulder which became severe. There were no objective signs of inflammation. Three days later the proximal phalangeal joint of the left index finger became swollen, painful and red, and the next day the corresponding joint of the left ring finger was similarly involved.

By the end of the third week in the hospital the temperature had gradually decreased to a daily maximum of 99.8°. The pulse and respirations still remained high, however, up to about 110 and 32 respectively. He still had a slight dry cough and sometimes on deep breathing a little pain just to the left of the sternum. The impairment of resonance and râles persisted at the right base, but the breath sounds had become much more nearly normal. By careful percussion an area of slight impairment of resonance extending about one finger's breadth to the left of the sternal border in the first and second interspaces could be made out, but there were no changes in breath sounds or râles over the left lung. The blood pressure in both arms had remained about 135 systolic and 90 diastolic. No abnormal pulsations of the chest wall, no thrills, no tracheal tug and no delay in either radial pulse could be detected. The eye grounds had been examined and had appeared normal. The glycosuria had been easily controlled by diet and insulin.

On the morning of May 3, about five weeks after the onset of illness, and three weeks after entering the hospital, the patient felt and appeared unusually well. At 11:30 a.m. while lying quietly in bed he began to cough up bright blood in large quantities. This continued and he bled to death within a half hour.

CLINICAL DIAGNOSIS

Mediastinal tumor (abscess, neoplasm, aneurysm?) with rupture either of the aorta or of a pulmonary vessel

Acute upper respiratory tract infection

Bronchopneumonia in the right lower lobe

Acute conjunctivitis
Acute polyarthritis
Diabetes mellitus
Atrophic rhinitis
Osteo-arthritis of dorsal vertebrae

DISCUSSION OF CLINICAL FEATURES

When this patient presented himself his picture was definitely that of an acute respiratory infection, rhinitis, pharyngitis, and bronchitis. The subsequent appearance of definite physical signs at the right base pointed to a pneumonic process. Roentgen-ray examination, however, showed only minimal involvement in this area but disclosed a massive lesion of some sort in or adjacent to the left border of the upper mediastinum. In the course of the disease, after the acute infection had subsided, it became apparent that this was the lesion of greatest significance and finally it seemed probable that death by rupture of a blood vessel was due to it.

As to the nature of this mass no definite diagnosis was made clinically. Abscess, neoplasm, and aortic aneurysm were considered.

The termination with rupture and profuse bleeding was highly suggestive of aneurysm. The roentgen-ray appearance, however, was not that of aortic aneurysm. The shadow was irregular in density and outline instead of showing a characteristic homogeneous sharp-edged appearance. None of the classical symptoms or signs of aneurysm were present. There was no history or evidence of syphilis, and the blood Wassermann was negative.

Mediastinal neoplasm might cause the roentgen-ray picture here seen. In fact the roentgenological appearance seemed most consistent with such a diagnosis, and the patient's age was in keeping.

Abscess of the mediastinum would explain the persistence of the symptoms, fever, leukocytosis, pain and the complicating conjunctivitis and polyarthritis and perhaps, though not typically, the roentgen-ray picture. The usual causes of mediastinal abscess, extension from a retro-pharyngeal or peritonsillar abscess, rupture of a caseous lymph node, or trauma were absent. Metastatic mediastinal abscesses from focal infection elsewhere in the body are rare. Mediastinal abscesses by extension from an influenzal pneumonia were fairly frequent during the epidemic of 1918 (McLester¹⁷), but such an etiology could not apply to the present case. The occurrence of frequent head and chest colds since the acute respiratory infection, similar to the present one which the patient had two years ago, suggested the possibility of a focal infection of the nasal sinuses, or possibly a bronchiectasis, from which one of the rare metastatic mediastinal abscesses might have originated.

We considered these possibilities without being able to make a definite diagnosis. The true pathology of the lesion shown in the roentgen-ray films was disclosed only by the autopsy.

PATHOLOGICAL FINDINGS

The autopsy was performed six and a half hours after death. The pathologic anatomical diagnosis was: Abscess of the arch of the aorta with rupture into the aortic lumen and into the left upper lobe. Sanguinous imbibition of the medial portion of the left upper pulmonary lobe. Atheromatosis of the aorta, of its larger branches and of the coronary arteries. Incipient cirrhosis of the liver. Multiple varices in the mucosa of the jejunum. Osteo-arthritis of the thoracic vertebrae with complete ankylosis.

A detailed description of the pertinent findings follows.

At the peripheral end of the aortic arch, the aorta is adherent to the left upper pulmonary lobe. In this region, there is a mass of the shape of a half sphere which, with its broad base, is firmly attached to the aorta, while its dome is attached to the

left upper lobe, it measures about 5 cm in its greatest diameter. The medial portion of the upper lobe is soggy and non-crepitant. After the aorta is opened on its anterior surface, a round hole is seen in the intima at the location of the mass between aorta and upper lobe. This hole has well defined, slightly depressed borders, and measures



FIG 2 Section through intima and part of the media near the point of perforation, showing chronic pyogenic foci invading and destroying the elastic fibers. Weigert's elastica stain, magnification approximately 100 \times .

1.5 cm in largest diameter. It leads into a cavum, extending through the aortic wall to a depth of about 1 cm. This cavum contains some dark blood clots. A section through the aortic wall and the left upper lobe through the center of the cavum, shows that the aortic wall reaches, without break and without thickening, to the margin of the hole and that the tissue adjacent to the aorta is markedly thickened, beginning 2 cm above the hole and extending 5 cm below the hole. In this whole extent, the aorta is adherent to the lung through flat thick adhesions in which a white firm layer, 1 to 3 mm thick is seen, parallel with the aortic wall. The thickened tissue extends in the form of a flat arch across the cavum, but it is perforated at the point

of greatest elevation forming an open tract leading from the aortic lumen through the cavum into the subpleural tissue of the left upper lobe. Water instilled into the left upper bronchus spurts out freely from a small bronchus directly adjacent to the pleural perforation. The pulmonary tissue in this region is dark red, apparently devoid of air and friable, some dark blood is easily pressed out from the parenchyma.

The intima of the entire aorta shows moderate atheromatosis without calcification and without ulceration. The cardiac valves show no gross changes, and there is no dilatation of the aorta. The other organs do not reveal any pertinent findings.

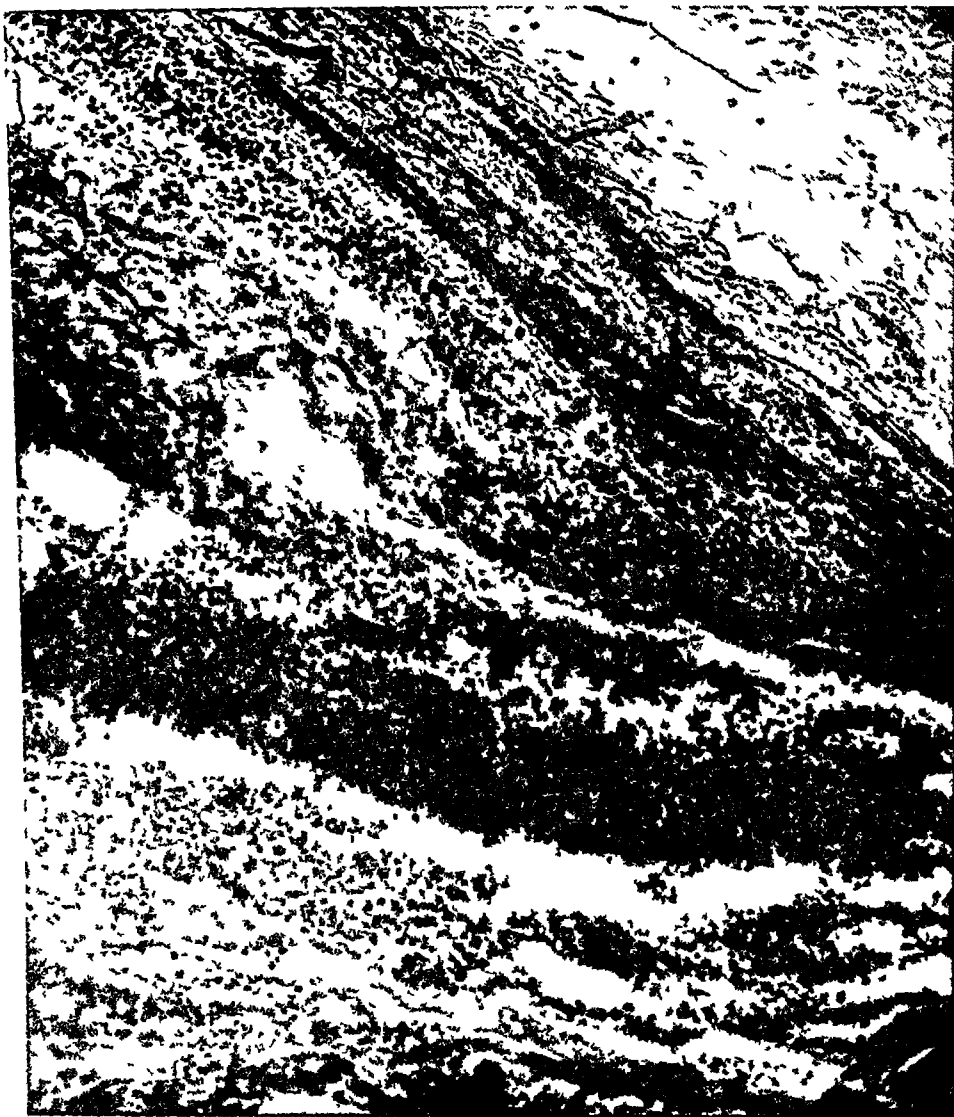


FIG. 3. Section through media and adventitia, showing massive pyogenic foci with complete destruction of elastic fibers. Weigert's elastica stain, magnification approximately $150\times$.

Histological Findings Sections through the aorta, adjoining the perforation, show the entire thickness of the aorta irregularly infiltrated with cells. There are dense accumulations of cells surrounding small areas of granular debris, rather rich in amorphous nuclear material, in such areas in the adventitial and median layers, the normal structures are completely effaced. In other areas there are dense cellular infiltrations without necrosis, and in still other ones, smaller accumulations of cells are included between separated elastic lamellae. (See figures 2 and 3.) The predominant

cells composing this exudate are fairly large mononuclear histiocytes, there are relatively few lymphocytes and plasma cells, and few polymorphonuclear cells (See figure 4) In the adventitial region, and bordering on the pleura, are more or less parallel strands of fibrous tissue which, however, are interspersed with exudate cells as described above The elastic fibers of the aorta are more or less separated by cellular exudate, and destroyed in regions of massive infiltration or necrosis (See figures

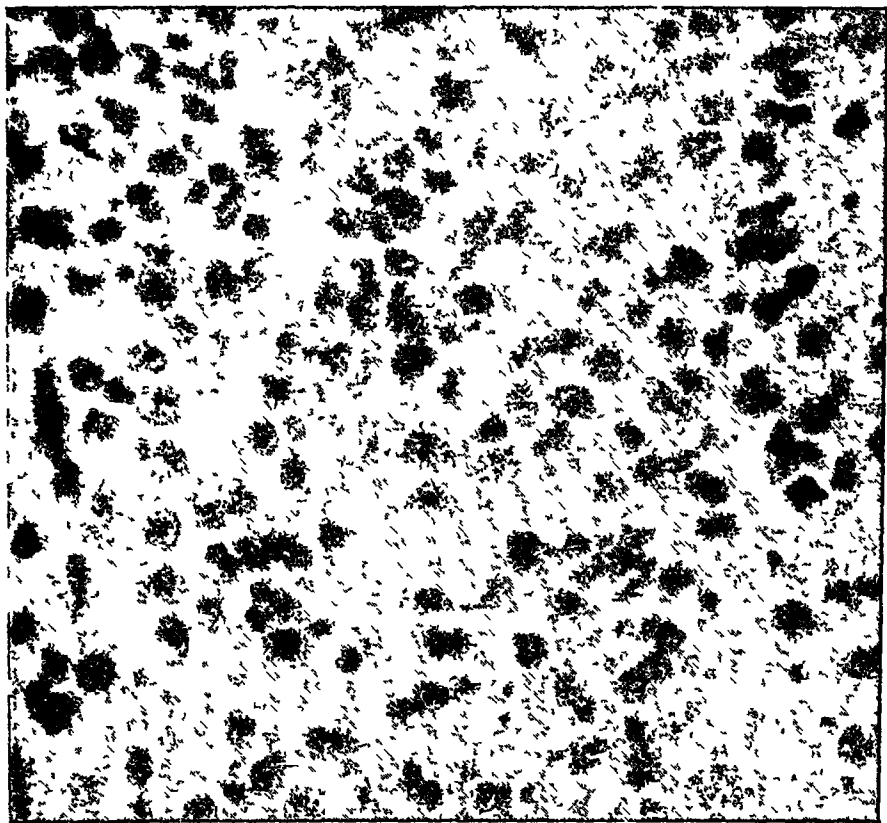


FIG 4 Section through a medial abscess, to show the type of cells present Hematoxylin-Eosin stain, magnification approximately 500 X

2 and 3) Sections taken at different levels show that more of the deeper elastic fibers are destroyed, and that the most superficial layers are absent only near the center of the lesions This suggests that the destruction advanced from the adventitia towards the intima, and the cellular infiltrations, too, indicate in their distribution the same order of development Near the perforation, cellular infiltrations and necrosis undermine for a distance of two to three millimeters well preserved elastic fibers, suggesting that the process advanced in the outer medial layer centrifugally before perforation occurred The elastic membrane of the pleura is destroyed in part and the adjoining pulmonary tissue shows slight cellular infiltration of the same character as the aortic wall In addition there is some compression of the parenchyma, slight perivascular peribronchial and interalveolar fibrosis, and many alveoli contain pale staining red cells

Gram stains failed to reveal any microorganisms in the foci either in aorta or lung No attempts were made to culture organisms from the lesion

Sections of the aorta at various levels, distant from the abscess, show intimal atheromatosis, but no pyogenic lesions

Histological studies of the other organs revealed no findings of significance

COMMENT

The patient died by exsanguination caused by the rupture of an abscess of the aortic wall into the aortic lumen and into the lung. In attempting to correlate the autopsy findings with the clinical course, it must be pointed out that the abscess is undoubtedly of longer duration than the patient's last acute illness. The relative chronicity of the abscess is indicated by the massive fibrosis on its pleural surface and by the fibrosis in the adjoining pulmonary tissue. It is questionable whether the rarity of polymorphonuclear leukocytes in the exudate can be used as an argument in the same direction, since other workers, as mentioned, have observed a similar preponderance of mononuclear exudate cells in the media of the aorta.

As to the location of the primary focus it has already been suggested in the discussion of the clinical features that the patient may have had a chronic focal infection in the respiratory tract. The appearance of the nasal mucous membrane suggested a chronic with a superimposed acute condition, and the roentgen-ray films of the nasal sinuses were in line with this. It is possible that a small metastatic abscess in the adventitia of the aorta, in the adjacent mediastinal tissues, or possibly in the lung itself, may have resulted from such a chronic focus. On this hypothesis the sequence of events would have been an acute infection, probably the one two years previous, a chronic focus following this, a later metastatic abscess in or adjacent to the aorta, with an exacerbation of this abscess by the acute respiratory infection preceding death, and its final rupture. In this exacerbation the complicating diabetes may also have been a factor.

Dr. R. H. Jaffé, in a personal communication, states that he has seen in influenza, purulent lymphangitis in the adventitia of the aorta. He suggests that the lesion presented here may have started as such a lymphangitis.

If such were the etiology in the present case, then the abscess may have originated during the attack of so-called influenza two years previously, doing away with the necessity of supposing any subsequent focal infection as its source. There is, however, no evidence that this attack was a true influenza.

These are mere conjectures, of course, and it is impossible to state definitely what was the primary source of the aortic abscess. In any event, it is obvious that the purulent aortic lesion did neither develop from the lumen, nor from infectious emboli in the vasa vasorum, but that it started either in the adventitia proper, or in tissue between the adventitia and the subpleural pulmonary parenchyma.

The last febrile illness of our patient, although apparently not caused by the aortic abscess, probably resulted in an exacerbation of that lesion; this caused the chronic abscess to perforate. It is likely that for some time preceding death, a seepage of blood from the aorta into the lung occurred, since the red cells in the lung were poorly stained, partly laked cells which could not have originated from the terminal hemoptysis. This sanguinous imbibition of the pulmonary tissue must be the cause of the roentgenological

shadow in the upper left pulmonic field, the abscess per se is far too small to be held responsible for this shadow

It would appear quite possible that the acute arthritic symptoms were caused by hematogenous propagation of the abscess contents

REFERENCES

- 1 AUERBACH, O Beiträge zur Kenntnis der eitrigen Aortitis, *Virchow's Arch f path Anat*, 1932, cclxxvi, 268-285
- 2 AWDEJEFF, M Ein Fall von perforierender Aortitis nach Scharlach, *Centralbl f allg Path u path Anat*, 1930, xlviii, 188
- 3 BUCHALY, J F Zur Pathogenese der perforierenden eitrigen Aortitis und ihrer Folgeerscheinungen, *Centralbl f allg Path u path Anat*, 1930, 1, 225-232
- 4 COOPER, P R A case of circumscribed ulceration of the thoracic aorta with fatal perforation into the left lung and pleura, *Med Chronicle*, 1914-1915, lix, 93-96
- 5 DESCLIN, L Über Aortitis thrombotica, *Frankf Ztschr f Path*, 1930, xl, 520-537
- 6 EDENHUIZEN, H Über zwei Fälle von mykotischem Aneurysma der Aorta mit Perforation in den Oesophagus, *Frankf Ztschr f Path*, 1915, xvi, 150
- 7 FOÀ, cited by WITTE³¹
- 8 HANSER, R Aortenruptur nach embolischem Lungenabszess, *Frankf Ztschr f Path*, 1919, xxii, 337-352
- 9 HAUSBRANDT, F Zwei Fälle von eitriger Aortitis, *Centralbl f allg Path u path Anat*, 1932, liii, 337-341
- 10 KAHLDEN, C V Über eine seltene Form der Aortenruptur, *Centralbl f allg Path und path Anat*, 1901, xii, 835-838
- 11 KORITSCHNER, R Beitrag zur Kenntnis der mykotischen Aortitis, *Centralbl f allg Path und path Anat*, 1912, xxiii, 100-106
- 12 LEVINSON, B Über tödliche Aortenzerreissung aus geringen Ursachen, *Virchow's Arch f path Anat*, 1931, cclxxxii, 1-29
- 13 LINDAU, A Aortitis gonorrhoeica ulcerosa, *Acta path et microbiol scandin*, 1924, 1, 263-275
- 14 LUZZATO, A R, cited by THOREL *Erg d allg Path*, (Abstract I), 1915, xviii, 1
- 15 MARESC, R Über eitrige Aortitis, *Wien klin Wchnschr*, 1926, xxxix, 1078-1088
- 16 MCCRAE, J A case of multiple mycotic aneurysms of the first part of the aorta, *Jr Path and Bact*, 1904, x, 373-379
- 17 MCLESTER, J S The diagnosis and treatment of disorders of metabolism, *Oxford Medicine*, Vol 2, 1928, Oxford University Press, New York, p 211
- 18 NAUWERCK, C, and EYRICH, H Zur Kenntnis der verrucosen Aortitis, *Beitr z pathol Anat und z allg Path*, 1889, v, 47-66
- 19 OETIKER, L Über akute Aortitis besonders als Komplikation der chronischen Erkrankungen der Aorta, 1924, B Schwabe and Company, Bâle
- 20 OLIVER, T A case of acute perforating or ulcerative aortitis in which the bacilli of anthrax were found, *Lancet*, 1891, ii, 1033-1035
- 21 ROKITSANSKY, K *Lehrbuch der pathologischen Anatomie*, Ed III, Vol II, 1856, W Braumüller, Wien, p 299
- 22 ROESNER Arrosion der Aorta als Typhuskompliation, *Berlin klin Wchnschr*, 1920, lvii, 667
- 23 SAPHIR, O, and COOPER, G W Acute suppurative aortitis superimposed on syphilitic aortitis, report of case, *Arch Path and Lab Med*, 1927, iv, 543-545
- 24 SCHEUER, H Aortenruptur bei Pyämie, *Berlin klin Wchnschr*, 1910, xlvii, 666-668
- 25 SCHLAGENHAUFER, F Über Aneurysmata per arrosionem, *Centralbl f allg Path und path Anat*, 1918, xxix, 421-424
- 26 SCHMORL, G Demonstration pathologisch-anatomischer Präparate, *Munch med Wchnschr*, 1914, lxi, 790-791

- 27 SIEGMUND, H Gefassveränderungen bei chronischer Streptokokkensepsis (Sepsis lenta), Centralbl f allg Path, 1924, xxxv, 276-277—Über nicht syphilitische Aortitis (Pathologisch-anatomische Demonstration zur Frage der Gefasswandveränderungen bei Allgemeininfektionen), Ztschr f Kreislaufforsch, 1929, xxi, 389-396
- 28 SPENGLER Entzündung der aufsteigenden Aorta, Virchow's Arch f path Anat, 1852, iv, 166-170
- 29 STUBLER, E Primäre akute Aortitis ulcerosa, Virchow's Arch f path Anat, 1921, ccxxxii, 126-133
- 30 STUMPF Über die akute Entzündung der Aorta, Beitr z pathol Anat und z allg Path, 1913, lvi, 417-440
- 31 WITTE, J Über Perforation der Aorta durch akute bakterielle Aortitis bei Pyämie, Beitr z path Anat und z allg Path, 1904-5, xxxvii, 151-161
- 32 ZALKA, E V Zwei Fälle von tuberkulöser Aortenperforation, Virchow's Arch f Path Anat, 1924, ccli, 685-698

THE PARENTERAL ADMINISTRATION OF MAGNESIUM SULPHATE IN HYPERTENSION *

By BURTON L. ZOEHMAN, M D , and BERNARD STERNBERG, M D ,
Brooklyn, New York

ALTHOUGH magnesium is an important component of all tissues, its proper place in the various processes in the body is but vaguely understood. Outside of the skeletal system where it is found in small quantities, it occurs in all the other organs of the body, at times in even greater quantities than calcium. By the method of Denis,¹ the blood stream contains quantities of magnesium ranging from 1.6 to 3.5 mg per 100 c c. Mathews² found it to be excreted in the urine to the amount of 1 gram per day as magnesium phosphate.

A number of interesting and important papers have appeared at intervals on the physiological effect of magnesium. Loeb³ in 1902, called attention to the depressant effect of magnesium and demonstrated its action in reducing muscular twitchings. Its ability to stop the tremors in tetany in cases of diminished calcium is clearly demonstrated. Beginning in 1908, Meltzer and Auer⁴ published a series of papers based on a number of experiments and again called attention to this unique action of magnesium. They showed that it has an anesthetic type of depressant action on animals when applied to the nerve trunk or when injected intravenously or subdurally. They demonstrated a marked effect on the involuntary musculature and on the various elements of the nervous apparatus.

It is the belief of a number of clinicians that magnesium salts are toxic if introduced into the circulation. Meyer and Gottlieb⁵ pointed out that only a few decigrams given at one time are sufficient to paralyze the respiratory center. Meltzer and Auer⁶ showed, on the other hand, that the toxicity of magnesium salts does not depend alone on the quantity of salt injected but also upon the speed with which the injection is given. They considered that 0.1 to 0.2 gm of the salt per kilo rabbit, is capable of completely abolishing the respiration and profoundly affecting the blood pressure when administered intravenously by rapid injection. On the other hand, a rabbit will apparently stand even as much as 1 gm per kilo if the intravenous injection is given with sufficient slowness. According to Solis-Cohen and Githens,⁷ if dogs are given M/1 solution at a rate of 1 c c per minute, the fatal dose per kilo is 2.86 c c corresponding to 0.224 gm of the dry sulphate. In rabbits, the respiration is stopped and the animal killed by 0.05 gm per kilo injected in 20 seconds but not by 0.25 gm in 12 minutes or by 0.75 gm in 60 minutes. They further assert that as much as 500 c c of a 2 per cent solution of magnesium sulphate may be

* Read before the Brooklyn Society of Internal Medicine May 26, 1933. Received for publication August 12, 1933.

given intravenously in man provided it is given slowly at the rate of about 10 c c per minute

Stander,⁸ in an effort to establish the toxicity level of magnesium sulphate experimentally, showed that magnesium sulphate in total doses ranging from 0.05 to 0.49 gm per kilo of body weight administered to dogs either intramuscularly or intravenously in 10 or 25 per cent solution, did not produce any marked changes in the blood on chemical examination but did produce histologic changes in the liver and kidneys in the form of moderate necrosis in the central part of the liver lobule and moderate degeneration in the convoluted tubules of the kidneys. He further stated, however, that in his opinion the non-toxic dose for human beings should not exceed 0.1 gm per kilo of body weight.

The antagonistic action of magnesium to calcium which increases the tone of the smooth musculature was observed by Meltzer and Auer.⁴ This interesting inter-relationship was further demonstrated by Mendel and Benedict⁹ in the increased elimination of calcium in the urine upon the intravenous injection of magnesium. That the body has a great tolerance for magnesium was shown by Joseph and Meltzer¹⁰ who reported the lethal dose in dogs as 223 gm of magnesium chloride per kilo of body weight. Matthews and Austin¹¹ in 1926, showed that 223 to 228 gm of hydrated magnesium sulphate ($\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$) per kilo is the fatal dose for the dog with a normal blood calcium. They further proved that this tolerance can be increased by the injection of calcium salts. During the same year, Woitaschewski¹² also called attention to its depressant effect. Matthews and Brooks¹³ in 1910, using magnesium sulphate, reported a drop in blood pressure in experimental animals. Consequently, in view of the observations of others in animals, it seemed desirable for us to demonstrate the effect of magnesium sulphate in the treatment of hypertension in man.

The application of a drug in the treatment of human ailments involves entirely different factors from those which are found in the experimental animal. In the first place, in the human subject with hypertension, we are dealing with an organism which is in a pathological state. Furthermore, the pathological state which presents itself with the symptom of hypertension is by no means a definite entity, dependent upon the same causes in each case. The pathogenesis of hypertension is still an unsolved question. We merely know that the varied factors which are likely to elicit hypertension include toxic states either of infectious or endogenous origin, metabolic or definitely endocrine disturbances, and finally, abnormal conditions of the central nervous system. Psychic factors also play a considerable rôle. It is frequently impossible to determine which of these factors is involved, moreover, a combination of several of these factors is not uncommon. Magnesium is a chemical capable of counteracting many of the forces enumerated in the complex pathogenesis of hypertension. Among these, two are most conspicuous—its ability to relax the smooth musculature and its sedative effect upon the nervous system.

Although in view of experiments in animals by others one can safely predict that the injection of magnesium will reduce the blood pressure in these experimental animals, this cannot be predicted with certainty in the human body in a state of hypertension because other factors may be present to counteract this action. In our experiments during the past year at the Kings County Hospital, in a series of 50 consecutive cases of hypertension, we found the depressing effect of magnesium upon the nervous state of the patient to be of value. This, surely, is not a factor encountered in the experimental animal.

Twenty-one cases of the series were hospital patients presenting a multiplicity of symptoms such as severe and persistent headache, insomnia, vertigo, hot flashes, buzzing in the ears and throbbing in the head. In many of our cases, these symptoms of hypertension were severe. Some of the patients showed, in addition to these symptoms, marked sclerosis of the peripheral blood vessels. Although no relief of these blood vessel changes could be expected from any treatment, these patients were not excluded from our series, in order to test the value of the procedure in an unselected series. The blood pressures in all of these cases were studied for a period of from one to several weeks before treatment with magnesium was attempted. This was done to study possible fluctuations in pressure with the patient at rest.

Twenty-nine of our series were Out-Patient Department cases who were taken off all medication for a period of seven days for the purpose of observation before the study of magnesium was started. Eighty per cent of these patients presented one or more of the symptoms of hypertension to a marked degree.

Fifteen of our patients showed evidence of nephritis, 32 showed atheromatous changes in the aorta—that is, widening of the aorta with a loud systolic murmur over the aortic area transmitted to the vessels of the neck. Thirty-five patients showed peripheral changes in the radial arteries, such as thickening and calcification. Retinal changes were observed in 24 of these individuals.

In this study, we were fully conscious of the difficulty of making definite observations and drawing definite conclusions when dealing with such a labile factor as blood pressure. In order to reduce the factors of error, we attempted to standardize our procedures. We therefore adopted the following routine: 1 Blood pressure readings were taken thrice daily for a period of a week on all hospital cases. On the Out-Patient Department cases, one single reading was taken each morning at the same hour, for a period of a week. 2 All injections were given at a definite hour in the morning. Ambulatory cases were rested in the supine position for a half hour before the injection was given, in a separate quiet room where all of our studies were made. 3 Blood pressure readings were made one, two and three hours after injection and every morning thereafter, at the same hour, for at least two weeks. 4 Three blood pressure readings were taken

at five minute intervals on all cases. The first reading was always discarded because we did not find it to be accurate, hence, we took the mean reading of the other two. It is needless to mention that the proper application of the cuff and a not too rapid inflation were carefully observed. All readings were taken by the same observer.

Preparation of Solution In making this study, we used chemically pure, anhydrous magnesium sulphate (Mallinckrodt) in triple distilled water. A stock solution of 25 per cent by weight was prepared. All dilutions were made from this immediately before using, by adding warm, sterile, triple distilled water. We can say that in the first 10 cases of our study we used 1/10 gm per kilo of body weight in the form of a 12½ per cent solution. We felt that this concentration was too great because of the marked subjective heat sensation in some of these patients. In our subsequent cases, we used a 2½ per cent solution injecting 0.35 gm per kilo of body weight, an amount which is well below the toxic dose reported for animals by others. Aside from one case of syncope which we encountered in our initial 10 cases when we employed a more concentrated solution of magnesium, our patients experienced no untoward reactions. This case of syncope was promptly relieved by an injection of adrenalin.

Technic of Injection A graduated salvarsan cylinder was used. A length of rubber tubing ended in an adapter for a luer needle. The rubber tubing was interrupted at a point 12 inches from the needle by a petcock so that the flow could be interrupted at any time upon complaint of the patient of excessive body heat. A twenty gauge needle of two inch length seemed to be ideal. The level of the fluid in the cylinder was kept at approximately 18 inches above the anterior chest wall of the patient at all times. The solution was warmed to body heat and was delivered to the patient intermittently in accordance with the sensation of heat experienced by the patient. The rate of flow of the solution was approximately a half hour per 100 c.c. The patient remained at rest in bed for two hours after the injection. The ambulatory cases were then permitted to go home.

We studied our cases from two points of view: (1) the effect of magnesium sulphate on the blood pressure, (2) the effect of magnesium sulphate on the subjective symptoms of the patient. We believe that the study of the latter is even more important than the study of the effect on the tension. It is a known fact, as has been observed in a great number of our cases, that the symptoms presented by patients with hyperpiesia are not in direct proportion to the degree of hypertension. Many patients are observed who have had high tensions for extended periods of time and yet have been able to attend to their usual duties without symptoms. These patients do not appear for treatment unless through some accidental finding, as a health or an insurance examination, the elevated blood pressure is discovered. The majority of the cases, however, complain of definite and distressing symptoms; hence, the relief of these symptoms is as important a factor in the treatment of hypertension as is the reduction in pressure itself.

TABLE I

Effect of Parenteral Administration of Magnesium Sulphate on Systolic Blood Pressure

Case Number	Blood Press before Injection	Average Drop in 1st 3 Hrs	Drop 1 Day After	Drop 2 Days After	Drop 3 Days After	Drop 4 Days After	Drop 5 Days After	Drop 6 Days After	Drop 7 Days After	Average Drop in 1st Week	Average Drop in 2nd Week
1	180	33	20	30	40	20	40	20	20	28	20
2	230	59	60	40	60	40	35	40	40	47	40
3	220	58	30	40	50	52	55	45	55	48	73
4	230	27	50	52	48	45	46	50	60	47	40
5	190	15	20	30	40	30	25	15	30	25	38
6	198	40	18	24	26	28	30	30	30	28	30
7	240	23	28	16	20	20	22	24	26	23	28
8	162	28	+12	+20	+12	+10	+14	+18	+16	+12	+20
9	170	17	5	5	+5	10	12	10	10	7	10
10	200	23	15	10	15	15	10	35	30	19	25
11	230	40	42	30	50	35	20	0	5	28	62
12	195	20	5	31	50	15	40	25	40	28	45
13	180	15	10	6	25	10	+5	10	15	14	23
14	200	11	15	+10	+20	5	+20	+35	+15	+9	+3
15	220	10	40	20	20	25	20	25	25	23	25
16	185	11	47	55	43	40	35	15	20	33	25
17	215	0	+5	+10	+5	+5	+19	+15	+16	+9	+13
18	260	20	20	15	30	30	30	30	25	25	30
19	248	25	23	20	20	25	30	38	35	27	33
20	240	+30	5	65	50	70	75	80	85	50	65
21	235	3	40	45	35	30	35	35	35	32	35
22	190	25	25	25	30	22	26	25	25	25	33
23	180	20	20	20	12	27	24	26	30	22	42
24	184	26	24	20	19	20	12	22	24	21	24
25	235	61	55	43	40	35	40	20	17	39	14
26	226	31	51	50	45	45	46	45	41	44	51
27	245	35	65	60	60	65	55	51	55	56	58
28	176	21	31	31	30	26	28	28	28	28	31
29	224	39	40	39	46	45	50	45	40	43	34
30	205	20	25	21	25	28	20	20	26	23	27
31	208	44	48	40	45	43	40	38	40	42	45
32	225	45	43	35	35	40	40	35	30	38	30
33	260	40	+5	40	44	40	42	40	35	34	35
34	212	27	37	47	45	40	45	48	45	42	50
35	188	40	38	35	40	34	36	32	18	34	19
36	170	30	26	22	25	22	30	20	26	25	28
37	212	32	37	38	42	54	50	52	47	44	37
38	260	55	75	72	74	84	82	80	74	74	76
39	200	55	35	36	58	54	40	45	46	46	44
40	165	30	17	+5	+10	+9	+15	+15	+20	+3	+25
41	220	56	70	55	60	65	65	54	65	61	61
42	180	20	25	20	12	12	20	18	20	18	23
43	205	30	40	41	50	40	41	45	40	41	40
44	178	33	35	38	40	43	35	38	35	37	38
45	185	15	+7	+9	13	10	15	10	0	6	15
46	185	5	5	5	25	20	20	20	20	15	15
47	194	20	64	50	45	39	26	34	40	40	44
48	210	55	50	40	40	45	40	42	42	44	40
49	175	19	31	30	30	25	20	20	25	25	19
50	190	25	25	25	30	22	26	25	25	25	33

+ indicates rise instead of fall in blood pressure

I EFFECT OF MAGNESIUM SULPHATE ON THE BLOOD PRESSURE

(A) *Effect on Systolic Pressure* From a summation of table 1, one finds that four cases showed an average rise ranging from three to 12 mm of mercury during the first week, four cases showed an average rise of three to 25 mm during the second week. Forty-six cases responded favorably with some fall of pressure. Eliminating all cases which did not show an average drop of 20 mm of mercury during the first week, there were 25 cases which showed an average drop of 21 to 40 mm and 15 cases with a fall more than 40 mm during the first week.

There were 26 cases which showed an average fall of 21 to 40 mm in the second week and 13 cases with a fall more than 40 mm. It will be noted that in the majority of cases, the fall in systolic pressure runs uniformly in the same cases during the two week period of study. In four cases (8, 14, 17 and 40) there was a fall in systolic pressure in the first three hours after injection, followed by a rise on the first or second day. This rise was sustained throughout the entire study. In one case (20), there was a marked rise of 30 mm within the first three hours with a subsequent marked and persistent fall of practically twice the initial rise. In two cases (33 and 45) slight rises of five and nine mm of mercury were noted within the first two days after injection with subsequent falls of 40 and 13 mm, respectively, which persisted throughout the study.

Table 2 illustrates the number of cases of the series with their respective falls in pressure on successive days of the study. The last column denotes the average fall during the second week of study. One readily recognizes

TABLE II
Summary of Effects of Magnesium Sulphate on Systolic Pressure

No of Cases Showing	3 Hours After Injection	1 Day After	2 Days After	3 Days After	4 Days After	5 Days After	6 Days After	7 Days After	2nd Week After
No drop	1	0	0	0	0	0	1	1	0
Drop 1-10	3	5	4	0	1	1	3	2	1
Drop 11-20	13	8	6	8	6	9	9	7	6
Drop 21-30	13	9	9	10	13	11	10	15	12
Drop 31-40	10	11	11	8	10	12	10	10	11
Drop 41-50	2	6	6	14	7	7	8	5	6
Drop 51-60	6	3	4	1	3	2	3	3	2
Drop 61-70	1	3	1	0	3	1	0	1	3
Drop 71-80	0	1	1	1	0	1	2	1	2
Drop 81-85	0	0	0	0	1	1	0	1	0
Rise	1	1	5	5	3	5	4	1	1

from this table the relative uniformity in the number of cases showing a constant fall in the systolic pressure throughout the period of observation

(B) *Effect on Diastolic Pressure* From a summation of table 3, one

TABLE III

Effect of Parenteral Administration of Magnesium Sulphate on Diastolic Blood Pressure

Case Number	Blood Press before Injection	Average Drop in 1st 3 Hrs	Drop 1 Day After	Drop 2 Days After	Drop 3 Days After	Drop 4 Days After	Drop 5 Days After	Drop 6 Days After	Drop 7 Days After	Average Drop in 1st Week	Average Drop in 2nd Week
1	120	25	20	30	10	20	25	20	20	21	18
2	130	30	25	25	15	10	12	14	12	18	10
3	135	14	15	5	0	15	30	25	45	19	43
4	110	9	10	12	12	10	10	8	8	10	8
5	120	15	15	15	20	20	20	20	20	18	20
6	62	+24	+10	+14	+2	+8	2	+2	+2	+8	+2
7	130	10	2	+2	2	+2	+2	4	6	2	6
8	78	7	2	+6	4	6	12	10	8	5	6
9	100	12	0	0	5	0	0	4	0	3	4
10	140	5	20	0	10	20	10	20	20	13	20
11	120	0	0	0	10	10	10	0	+20	1	8
12	90	0	+5	2	+10	+5	+5	0	0	+4	+5
13	105	5	+5	+5	5	+15	+15	+5	15	+2	5
14	120	10	10	0	+10	+20	+30	+25	+5	+9	+4
15	120	+5	+5	0	+10	+10	+8	+10	+10	+7	+10
16	110	22	30	34	20	40	34	35	30	31	28
17	120	+10	10	+10	+10	+10	0	20	+8	+2	+10
18	150	20	20	0	0	24	0	10	10	11	10
19	125	15	13	10	10	10	8	5	5	10	8
20	140	0	5	30	30	30	20	30	30	21	25
21	130	+2	5	0	20	4	15	10	15	8	13
22	100	+5	0	0	+4	+5	+10	+10	+10	+6	+15
23	95	+6	5	5	13	7	14	12	11	8	11
24	118	3	+2	+6	+4	+2	+4	+2	0	+2	+1
25	130	27	15	12	10	12	10	10	8	13	5
26	116	18	1	8	11	14	16	13	11	12	12
27	130	0	20	15	15	15	18	15	20	15	18
28	108	3	16	10	9	3	8	14	14	10	10
29	108	+2	+4	+7	0	+5	+4	+7	+9	+5	+7
30	120	0	4	2	8	6	5	5	10	5	12
31	104	24	14	10	15	19	10	6	10	14	12
32	115	10	3	20	20	15	20	15	20	15	15
33	160	40	30	25	20	25	25	20	30	27	20
34	120	0	10	25	20	15	20	10	15	14	0
35	100	2	8	10	15	10	20	12	8	11	10
36	104	14	14	16	12	4	14	9	15	12	14
37	80	+5	+5	+10	+10	+4	+8	+10	+5	+7	+3
38	154	4	4	14	18	29	20	19	20	16	35
39	95	13	10	7	20	15	11	20	21	15	15
40	105	20	5	5	5	5	5	10	12	9	15
41	110	20	35	25	20	30	20	22	20	24	25
42	95	0	10	10	10	15	10	15	15	11	22
43	115	5	10	10	10	15	10	15	10	11	10
44	94	4	5	2	8	12	7	6	12	7	7
45	115	5	3	5	5	8	5	7	0	5	5
46	90	0	0	+5	20	15	15	10	5	8	5
47	110	10	15	20	10	12	10	10	10	12	10
48	110	15	15	10	15	15	17	18	20	14	20
49	90	6	12	16	18	18	20	15	20	16	20
50	100	+5	0	0	+5	+4	+10	+10	+10	+6	+15

+ indicates rise instead of fall in blood pressure

finds that 11 cases showed an average rise during the first week ranging from two to nine mm of mercury and 10 cases showed an average rise from one to 15 mm of mercury during the second week. Thirty-nine cases responded with some fall in diastolic pressure during the first week and 40 cases during the second week, as follows: discounting all falls below 10 mm of mercury, 20 cases responded with an average fall from 11 to 20 mm and five cases with an average fall from 21 to 31 mm of mercury during the first week.

During the second week, 16 cases responded with an average fall of 11 to 20 mm of mercury and five cases responded with a fall ranging between 21 and 43 mm of mercury.

Table 4 illustrates the number of cases of the series with their respective

TABLE IV
Summary of Effects of Magnesium Sulphate on Diastolic Pressure

No of Cases Showing	3 Hours After Injection	1 Day After	2 Days After	3 Days After	4 Days After	5 Days After	6 Days After	7 Days After	2nd Week After
No drop									
0-5	17	17	16	9	5	7	6	6	6
Drop									
6-10	7	8	9	11	9	11	13	10	12
Drop									
11-15	7	9	5	9	13	7	10	11	9
Drop									
16-20	4	5	4	11	5	11	8	9	7
Drop									
21-25	3	1	4	0	2	2	2	1	3
Drop									
26-30	2	2	2	1	3	1	1	3	1
Drop									
31-35	0	1	1	0	0	1	1	0	1
Drop									
36-40	1	0	0	0	1	0	0	0	0
Drop									
41-45	0	0	0	0	0	0	0	1	1
Rise	9	7	9	9	12	10	9	9	10

falls in diastolic pressure on successive days of the study. The last column denotes the average fall during the second week of study. It is quite apparent from this table that the number of cases showing a constant fall in the diastolic pressure throughout the period of observation is fairly consistent.

II. EFFECT OF MAGNESIUM SULPHATE ON THE SYMPTOMS OF HYPERTENSION

The patients who came under our care did not come seeking relief from their hypertension; they came because they were suffering from a number of annoying and persisting symptoms. Our own observations, which coincide with those of other authors, disclose the fact that the following symptoms

are most commonly encountered in hypertension (1) headache, (2) insomnia, (3) vertigo, (4) hot flashes, (5) head noises, and (6) nervousness

Headache was the most prominent symptom occurring in 36 cases. Eighteen of these cases experienced complete relief for a period of two weeks after a single injection of 0.35 gm of magnesium sulphate per kilo of body weight. Ten cases experienced moderate relief for a similar period. Six experienced relief for a period longer than four weeks. Two cases were not relieved at all.

Insomnia was the next most frequent symptom complained of. This symptom was found in 30 of our cases. Eighteen of these cases experienced relief for a period of two weeks after the first injection. In the greater number of these cases that were greatly disturbed by restlessness with only two or three hours of sleep per night, it was found that after injection they were able to have a good night's rest of seven to nine hours sleep. Three cases experienced relief for more than two weeks. Seven cases experienced moderate relief and two cases had no relief.

Vertigo Twenty-seven cases of the series complained of vertigo. Nineteen were relieved for two weeks after the first injection. Three cases were relieved for a period longer than two weeks. Five cases had moderate relief.

Hot Flashes Twenty cases complained of hot flashes. Ten were relieved for a period of two weeks after the first injection. Five cases were relieved for a longer period. Four cases were relieved only moderately. One case was not relieved.

Head Noises Ten cases of our series complained of head noises which include buzzing in the ears. Six were relieved for a period of two weeks after the first injection. Two cases were relieved for a period longer than two weeks. Two cases were relieved for one week only.

Nervousness Fifteen cases complained of nervousness. Nine were relieved for a period of two weeks after the first injection. Four cases were relieved for a longer period than two weeks. Two were only moderately relieved.

It is interesting to note that most patients complained of a multiplicity of symptoms. When the injection of magnesium sulphate produced relief, there was an amelioration of all the symptoms experienced by the patient. The effect of magnesium sulphate upon the blood pressure did not run parallel in a great number of cases with the relief of symptoms because where there was no marked, or only a moderate effect on the blood pressure, there was a considerable amelioration of symptoms.

CONCLUSIONS

1 The parenteral administration of magnesium sulphate had a distinct effect in reducing the systolic pressure in 40 cases of a series of 50 consecutive cases of hypertension. The effect was sustained for a period of at least two weeks.

2 The parenteral administration of magnesium sulphate had a definite effect in reducing the diastolic pressure in 25 cases of the same series and the effect was sustained for a period of two weeks in 21 cases

3 The parenteral administration of magnesium sulphate had a distinct ameliorating effect on the symptoms of hypertension, viz, headache, vertigo, insomnia, hot flashes, head noises and nervousness

Our thanks are due Dr William Stimpson Hubbard and Dr Benjamin Frank Corwin through whose cooperation this work was made possible

BIBLIOGRAPHY

- 1 DENIS, W Determination of magnesium in blood, *Jr Biol Chem*, 1920, xli, 363-365
- 2 MATHEWS, A P Physiological chemistry, a textbook and manual for students, 5th ed, 1930, William Wood and Company, New York, p 799
- 3 LOEB, J On the production and suppression of muscular twitchings and hypersensitivity of the skin by electrolytes, *The Decennial Publications, University of Chicago*, 1902, x, 1-13
- 4 MELTZER, S J, and AUER, J The antagonistic action of calcium upon the inhibitory effect of magnesium, *Am Jr Physiol*, 1908, xxi, 400-419
- 5 MEYER, H H, and GOTTLIEB, R Pharmacology, clinical and experimental, 2nd ed, 1926, J B Lippincott and Company, Philadelphia, p 221
- 6 MELTZER, S J, and AUER, J Physiological and pharmacological studies of magnesium salts II The toxicity of intravenous injections, in particular the effects upon the centers of the medulla oblongata, *Am Jr Physiol*, 1906, xv, 387-405
- 7 SOLIS-COHLN, S, and GITHENS, T S Pharmacotherapeutics, materia medica and drug action, 1928, D Appleton and Company, New York, p 1721
- 8 STANDER, H J Effect of intravenous administration of magnesium sulphate, experimental studies, *Jr Am Med. Assoc*, 1929, xcii, 631-636
- 9 MENDL, L B, and BENEDICT, S R The paths of excretion for inorganic compounds I-IV The excretion of magnesium, *Am Jr Physiol*, 1909, xxv, 1-22
- 10 JOSEPH, D R, and MELTZER, S J The comparative toxicity of the chlorides of magnesium, calcium, potassium and sodium, *Jr Pharm and Exper Therap*, 1909-10, i, 1-26
- 11 MATTHEWS, S A, and AUSTIN, W C Effect of blood calcium level on tolerance to magnesium, hypercalcemia induced by parathyroid hormone, *Am Jr Physiol*, 1927, lxxix, 708-718
- 12 WOITASCHIEWSKI, J B Experimentelle Untersuchungen und klinische Beobachtungen über die Wirkung schwefelsaurer Magnesia, *Arch f klin Chir*, 1926, cxli, 135-150
- 13 MATTHEWS, S A, and BROOKS, C On the action of magnesium sulphate, *Jr Pharm and Exper Therap*, 1910, ii, 87-99

EXPERIMENTAL AND CLINICAL STUDIES OF ERGOTAMINE

V. THE ACTION OF ERGOTAMINE ON THE SYMPATHETIC NERVOUS SYSTEM STIMULATED BY EPINEPHRINE STUDIES OF THE METABOLIC RATE, PULSE RATE, BLOOD PRESSURE, BLOOD SUGAR AND THE TOTAL LEUKOCYTE COUNT *

By JOHN B. YOUMANS, M D , F A C P , CHARLES TRABUE, M D , and
RALPH S. BUVINGER, M D , with the Technical Assistance of
HELEN FRANK, B A , *Nashville, Tennessee*

IN A PREVIOUS PAPER ¹ it was shown that in human subjects, under basal conditions, ergotamine had little or no effect on those motor divisions of the sympathetic nervous system concerned with the regulation of the blood sugar level or the basal metabolic rate. Evidence was given for the belief that the slowing of the pulse was the result of vagus stimulation rather than depression of the sympathetic. It was suggested at that time that the failure of ergotamine to depress certain of these motor functions of the sympathetic nervous system might be explained if the latter were inactive ² in the basal state and therefore either insusceptible to the action of ergotamine or incapable of exhibiting its effect. Therefore, it was decided to study the action of ergotamine on the sympathetics which had been stimulated by epinephrine.

METHODS

The subjects were young healthy adults many of whom had served as subjects in previous experiments with ergotamine and were accustomed to the procedures employed. Observations were made of the combined effects of the drugs on the blood sugar level, metabolic rate, pulse rate, blood pressure and total leukocyte count. The following plan was followed. Six hours after a light breakfast the subject was placed in bed and allowed to rest quietly for at least an hour. Following the rest period there was a preliminary period during which the pulse rate and blood pressure were determined at frequent intervals until a basal level was reached. At the end of this time the basal metabolic rate was determined and a sample of blood drawn for determination of the blood sugar. In the studies of the leukocyte count, which were made separately, successive counts were made at the end of the rest period until a basal level was reached. After a short rest to allow the subject to recover from these procedures, epinephrine (0.5 or 1.0 mg. intramuscularly) and ergotamine (0.5 mg. subcutaneously) were injected and the metabolic rate, pulse rate, blood pressure, blood sugar

* Received for publication March 6, 1933.

From the Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee.

concentration and total leukocyte count were determined at suitable intervals. In some of the subjects separate studies were made to compare the effect of ergotamine when given before the epinephrine with its effect when given after. In the others the ergotamine was given either before or after the epinephrine. When ergotamine was given first the time interval between the injection of ergotamine and epinephrine was approximately 10 to 15 minutes to allow the ergotamine to develop its effect. When the epinephrine was injected first the ergotamine was given immediately afterwards. In all cases control studies were made of the effect of epinephrine and of ergotamine alone.

The metabolic rate was determined by means of a spirometer and an analysis of the expired air (Haldane). The pulse was counted with a stop watch, when possible it was counted for a full minute. The blood pressure was determined with a mercury sphygmomanometer by the auscultatory method. Determinations of the blood sugar were made according to the method of Folin³. All the leukocyte counts were made by a single observer, using special pipettes and counting chamber calibrated by the Bureau of Standards. The same pipettes and chamber were used throughout the experiments. Duplicate counts were made at each period and repeated unless they checked closely.

TABLE I

The Effect of Ergotamine (0.5 mg Subcutaneously) on the Response of the Metabolic Rate to Injections of Epinephrine

Subject	Metabolic rate before injection per cent	Metabolic rate after injection* per cent			
		15 min	30 min	60 min	120 min
J Y (1.0 mg epinephrine)					
Epinephrine control	-12	+30	+26	+18	+3
Ergotamine—Epinephrine	-17	+41	+11	-4	-18
Epinephrine—Ergotamine	-7	+6	+13	+9	±0
W F (1.0 mg epinephrine)					
Epinephrine control	-7	+37	+32	+23	+1
Ergotamine—Epinephrine	+2	+27	+38	+25	+5
Epinephrine—Ergotamine	-3	+18	+18	+18	+4
H F (1.0 mg epinephrine)					
Epinephrine control	-5	+20	+35	+21	+1
Ergotamine—Epinephrine	-6	+22	+32	+30	+1
Epinephrine—Ergotamine	+1	+8	+22	+28	+11
M F (0.5 mg epinephrine)					
Epinephrine control	+16	+24	+22	+28	+17
Epinephrine—Ergotamine	+8	+22	+23	+29	+15
I P (0.5 mg epinephrine)					
Epinephrine control	+7	+17	+25	+15	+1
Epinephrine—Ergotamine	±0	+18	+25	+15	-1
W S (0.5 mg epinephrine)					
Epinephrine control	-5	-2	+6	+13	-6
Ergotamine—Epinephrine	-2	+16	+25	+13	-7

* The drugs were given in the order named in the various experiments. The time refers to the per cent after the injection of epinephrine. When the epinephrine was given first the time of the ergotamine was noted immediately afterward. When the ergotamine was injected first a time of 10 to 15 minutes elapsed before the injection of epinephrine.

RESULTS

The results are summarized and shown graphically in the accompanying tables and charts. The effect on the metabolic rate was studied in six subjects, three of whom were given 1 mg and three 0.5 mg of epinephrine each. When the ergotamine was given *after* an injection of 1 mg of epinephrine, the metabolic rate failed to increase as greatly as when the same amount of epinephrine was given alone. When ergotamine was injected *before* the epinephrine it failed to modify the effect of the latter, except that in one subject the metabolic rate fell to the initial level sooner than when epinephrine alone, or epinephrine followed by ergotamine, was given. Of the three subjects who were given 0.5 mg of epinephrine two were given ergotamine after the epinephrine and one before. In the former ergotamine had no influence on the increase in metabolic rate caused by the epinephrine, while in the latter the rate was higher after the injection of both drugs than after epinephrine alone (table 1, figure 1).

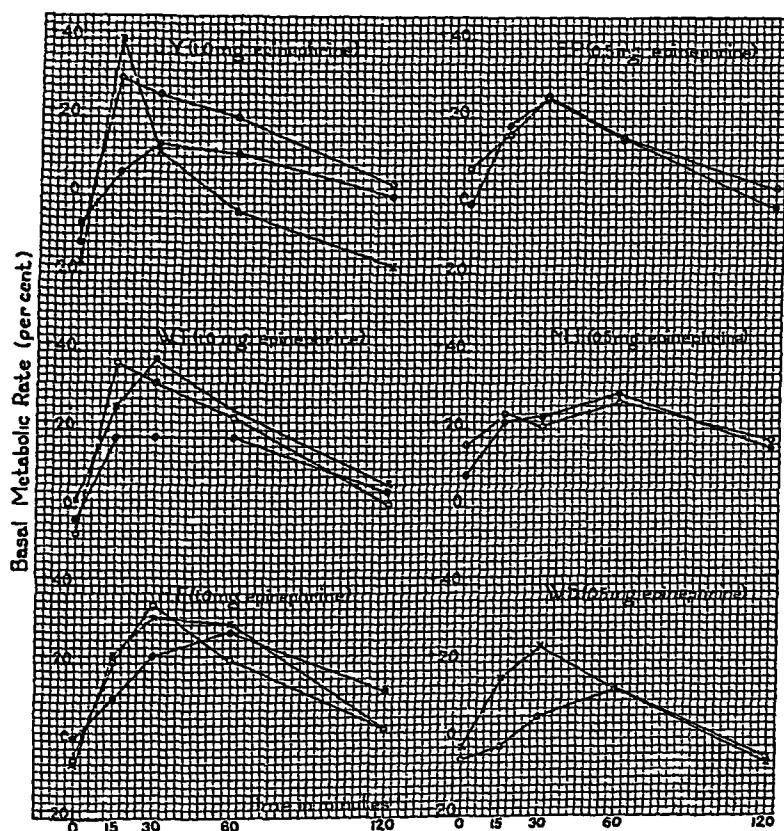


FIG 1 The effect of ergotamine (0.5 mg subcutaneously) on the response of the basal metabolic rate to an injection of epinephrine. The open circles represent experiments in which epinephrine alone was given, the crosses, those in which the ergotamine was given before the epinephrine, and the solid dots, those in which epinephrine was injected before the ergotamine. The initial values are those obtained before the injections. The time refers to the intervals after the injection of epinephrine. When epinephrine was injected first, the ergotamine was given immediately afterwards. When ergotamine was injected first, a period of 10 to 15 minutes elapsed before the injection of epinephrine.

In six subjects the effect of ergotamine on the hyperglycemic response to the injection of epinephrine was irregular but resembled somewhat its effect on the metabolic rate (table 2) Because of the variation in the basal

TABLE II

The Effect of Ergotamine (0.5 mg Subcutaneously) on the Hyperglycemia Caused by an Injection of Epinephrine

Subject	Blood sugar before injections mg per 100 c c	Blood sugar (mg per 100 c c) after injection*			
		15 min	30 min	60 min	120 min
J Y (1.0 mg epinephrine)					
Epinephrine control	73	95	105	105	114
Ergotamine—Epinephrine	92	91	102	133	115
Epinephrine—Ergotamine	95	100	107	87	
W T (1.0 mg epinephrine)					
Epinephrine control	73	93	114	121	108
Ergotamine—Epinephrine	92	91	101	133	114
H. F (1.0 mg epinephrine)					
Epinephrine control	67	190	133	153	118
Epinephrine—Ergotamine	67	89	94	138	149
M T (0.5 mg epinephrine)					
Epinephrine control	71	77	82	115	93
Epinephrine—Ergotamine	68	68	81	115	108
E P (0.5 mg epinephrine)					
Epinephrine control	75	69	93	76	74
Epinephrine—Ergotamine	71	89	105	105	82
W S (0.5 mg epinephrine)					
Epinephrine control	77	80	89	118	105
Ergotamine—Epinephrine	73	105	105	95	91

* The drugs were given in the order named in the various experiments. The time refers to the interval after the injection of epinephrine. When the epinephrine was given first the ergotamine was injected immediately afterward. When the ergotamine was injected first a period of 10 to 15 minutes elapsed before the injection of epinephrine.

level of the blood sugar in the different experiments the effect of ergotamine is best determined by comparing the increase over the initial level in each experiment (figure 2). Thus compared, the hyperglycemic effect of 1 mg of epinephrine was somewhat less when ergotamine and epinephrine were given than when the same amount of epinephrine was given alone. In the subject (J B Y), in whom the effect of ergotamine given before and after the epinephrine was compared, the inhibiting effect of ergotamine was greater when it was given after the epinephrine. When ergotamine was injected before the epinephrine there was an early inhibition of the hyperglycemia followed by an increase in the blood sugar at the one hour period to as high a level as occurred after epinephrine alone, but a more rapid return toward the initial level. In subject H. F. the injection of ergotamine after epinephrine resulted in a smaller increase than with epinephrine alone, except that at the end of two hours the blood sugar was higher than at the end of an hour and was above the level reached in the control study.

at the same period. Little effect of the ergotamine was noted in the three subjects who were given 0.5 mg of epinephrine. In one (E. P.) the rise in blood sugar was slightly greater after both ergotamine and epinephrine than after epinephrine alone.

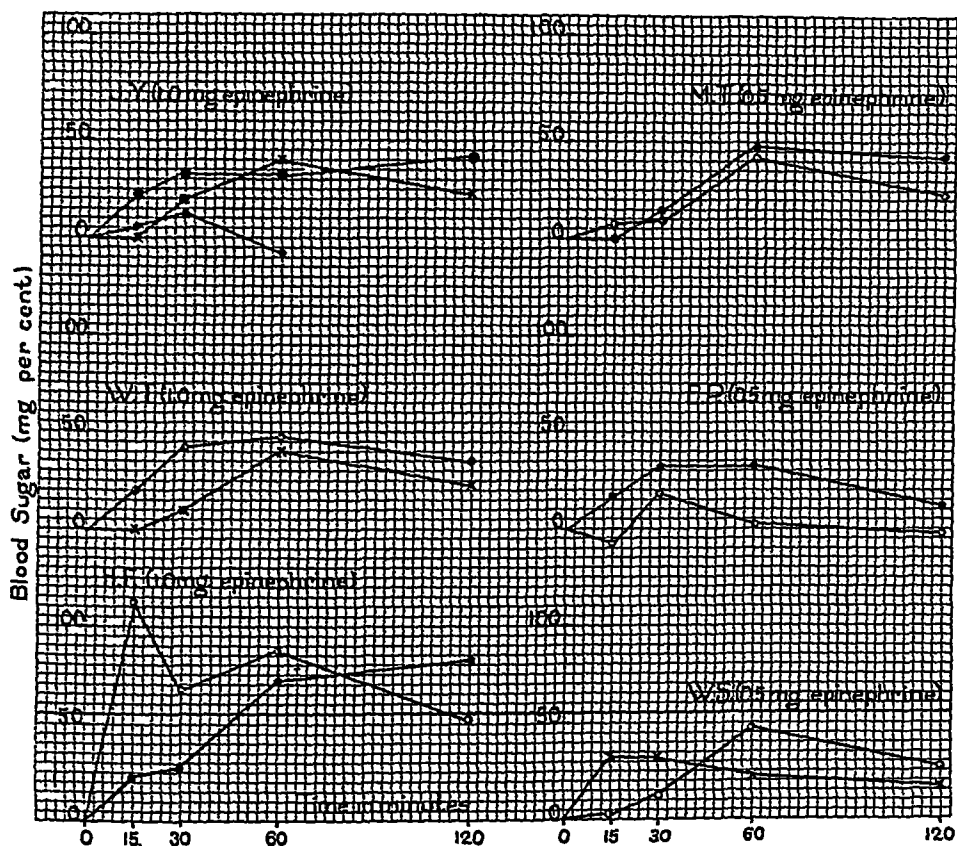


FIG. 2 The effect of ergotamine (0.5 mg subcutaneously) on the hyperglycemia caused by an injection of epinephrine. In this figure the differences between the initial values and those found after injection are plotted rather than the actual values, the initial value in each case being taken as zero. The open circles represent experiments in which epinephrine alone was given, the crosses those in which ergotamine was given before the epinephrine, the solid dots, those in which epinephrine was injected before the ergotamine. The time refers to the intervals after the injection of epinephrine. When epinephrine was injected first, the ergotamine was given immediately afterwards. When ergotamine was given first a period of 10 to 15 minutes elapsed before the injection of epinephrine.

There is a difference in the time after injection at which the effect of ergotamine and epinephrine on the pulse rate occurs. This makes it difficult to determine the influence of ergotamine on the action of epinephrine. In four of the six subjects the maximum pulse rate after the injection of epinephrine was somewhat less when ergotamine was given irrespective of whether the latter was given before or after the epinephrine (table 3). Furthermore, there was in general a tendency for the pulse rate to return to the basal level sooner and for the maximum pulse rate to be reached earlier after the injection of epinephrine when ergotamine was given. The latter finding is of no significance, however, being due simply to the failure

of the pulse rate to rise as high when ergotamine was given, the maximum consequently being reached earlier. In one subject the increase in pulse rate was greater when ergotamine was given before the epinephrine than

TABLE III

The Effect of Ergotamine on the Response of the Pulse Rate to an Injection of Epinephrine

Subject	Epinephrine Control			Ergotamine— Epinephrine*			Epinephrine— Ergotamine*		
	Basal pulse rate	Maximum pulse rate after injection	Time after injection	Basal pulse rate	Maximum pulse rate after injection of epinephrine	Time after injection of epinephrine	Basal pulse rate	Maximum pulse rate after injection of epinephrine	Time after injection of epinephrine
	Beats per min	Beats per min	Min	Beats per min	Beats per min	Min	Beats per min	Beats per min	Min
J. Y (1 mg epinephrine)	66	102	26	65	96	5	71	96	13
W T (1 mg epinephrine)	73	100	24	71	90	14	76	96	16
H F (1 mg epinephrine)	71	116	37	75	108	30	75	102	34
M T (0.5 mg epinephrine)	68	88	11				65	80	12
W S (0.5 mg epinephrine)	69	84	55	60	88	8			
E P (0.5 mg epinephrine)	64	80	4				62	80	4

* The drugs were given in the order named. When the epinephrine was given first the ergotamine was injected immediately afterward. When the ergotamine was given first an interval of 10 to 15 minutes elapsed before the injection of epinephrine.

when epinephrine was given alone, and in one the increase in the pulse rate was the same when epinephrine alone and epinephrine and ergotamine were given. Both of these subjects were given 0.5 mg of epinephrine. In the experiments in which the ergotamine was given before the epinephrine a slowing of the pulse often occurred before the epinephrine was injected.

In six subjects the rise in diastolic blood pressure was greater when ergotamine and epinephrine were given than when epinephrine was given alone. The same was true of the systolic pressure except in one subject in whom the rise was the same in both experiments (table 4). The diastolic pressure showed relatively the greater increase. In general the rise was progressive following the injections, but in several instances there was a temporary drop in diastolic pressure below the initial level, usually occurring before the increase. This fall in pressure was not caused solely by the ergotamine, either directly or by modifying the action of epinephrine, since it occurred nearly as often when epinephrine alone was given.

TABLE IV

The Effect of Ergotamine (0.5 mg Subcutaneously) on Response of the Blood Pressure to an Injection of Epinephrine

Subject	* Maximum Blood Pressure (mm Hg)											
	Epinephrine control				Ergotamine— Epinephrine*				Epinephrine— Ergotamine*			
	Basal		After epinephrine injection		Basal		After epinephrine injection		Basal		After epinephrine injection	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
J Y (1 mg epinephrine)	98	68	122	70	88	62	122	75	98	65	144	85
W T (1 mg epinephrine)	104	64	140	66	100	66	152	74	102	60	144	78
H F (1 mg epinephrine)	118	72	156	76	120	70	156	82	120	70	156	76
M T (0.5 mg epinephrine)	100	60	108	66					96	58	130	78
W S (0.5 mg epinephrine)	114	70	124	74	106	70	134	80				
E P (0.5 mg epinephrine)	106	64	122	66					100	62	130	66

* The drugs were given in the order named. When the epinephrine was given first the ergotamine was injected immediately afterward. When the ergotamine was given first a period of 10 to 15 minutes elapsed before the injection of epinephrine.

In four subjects ergotamine alone had little effect on the total leukocyte count but in one the count was lowered slightly, and in another there was an increase which was not as great, however, as occurred with epinephrine. There was a slight tendency for ergotamine to inhibit the increase in leukocytes which followed the injection of 0.5 mg of epinephrine (table 5), but this effect is less marked when the results are compared on the basis of the increase over the initial level (figure 3). When comparison is made in the latter manner there is no constant relation between the effect of ergotamine and the time of its injection. In each of the four subjects ergotamine caused a partial inhibition of the rise in leukocytes following the injection of epinephrine in one or the other of the two experiments in which both drugs were given, but in some it occurred when the ergotamine preceded and in others when ergotamine followed the epinephrine. In some of the experiments the injection of both drugs caused a greater rise than occurred with epinephrine alone.

TABLE V

The Effect of Ergotamine (0.5 mg Subcutaneously) on the Leukocytosis Caused by the Injection of Epinephrine

Subject	Total leukocyte count before injections	Total leukocyte count after injections*					
		15 min	30 min	45 min	60 min	120 min	
H F	Epinephrine control	7,350	8,800	10,320	11,300	10,580	6,760
	Ergotamine control	7,260	8,180	8,320	7,580	8,040	8,140
	Ergotamine—Epinephrine	8,360	11,040	10,360	9,880	9,400	7,240
	Epinephrine—Ergotamine	6,140	8,960	9,160	8,680	8,240	6,600
A C	Epinephrine control	6,710	7,280	9,220	9,380	8,480	6,920
	Ergotamine control	5,280	4,100	4,260	4,580	5,260	5,420
	Ergotamine—Epinephrine	5,675	7,075	7,650	8,975	7,720	7,500
	Epinephrine—Ergotamine	5,425	7,475	6,300	5,825	5,750	5,750
G O	Epinephrine control	7,650	11,800	10,780	10,420	9,160	8,720
	Ergotamine control	8,500	9,080	8,420	8,740	8,160	8,350
	Ergotamine—Epinephrine	7,425	15,150	12,425	9,650	9,000	7,450
	Epinephrine—Ergotamine	7,860	11,225	8,625	8,750	8,675	6,450
F. T	Epinephrine control	5,680	7,440	7,760	7,600	6,120	6,080
	Ergotamine control	4,830	4,600	6,275	6,525	6,225	5,820
	Ergotamine—Epinephrine	7,440	7,595	8,275	7,350	7,225	5,700
	Epinephrine—Ergotamine	5,640	7,100	8,375	7,875	7,350	5,675

* The drugs were given in the order named in the various experiments. When both drugs were given the time refers to the interval after the injection of epinephrine. When the epinephrine was injected first the injection of ergotamine followed immediately. When ergotamine was given first an interval of 10 to 15 minutes elapsed before the injection of epinephrine.

DISCUSSION

It is evident that under the conditions of these experiments ergotamine may inhibit slightly the stimulating action of epinephrine on some functions of the sympathetic, but the inhibition is irregular and far from complete. Few similar studies have been reported and they deal only with the pulse rate and the blood sugar. Goldman² was unable to abolish or reverse the effect of epinephrine on the pulse rate with ergotamine. According to Moratti³ the increase in blood sugar caused by epinephrine is diminished (or prevented²) by ergotamine. A similar effect is reported by Coelho and de Oliveira.⁴ Others have reported contradictory results in conditions such as thyrotoxicosis in which a stimulation of the sympathetic may be present. These reports have been summarized by us in an earlier paper.¹ In our experiments on dogs² ergotamine was found to have less effect on the epinephrine hyperglycemia than was observed in the present study.

The effect of the two drugs on the blood pressure is most probably one of summation of individual reactions. We have shown that under basal conditions ergotamine increases the blood pressure,¹ the diastolic pressure principally. It is probable that this is the result of a direct action on the

vessels.¹ Epinephrine causes mainly an increase in systolic pressure. The observed effect of the two drugs is therefore similar to what would be expected from the effect of each alone. In animals, and with relatively much larger doses, ergotamine may neutralize or reverse the effect of epinephrine on the blood pressure. No such effect was observed in these experiments.

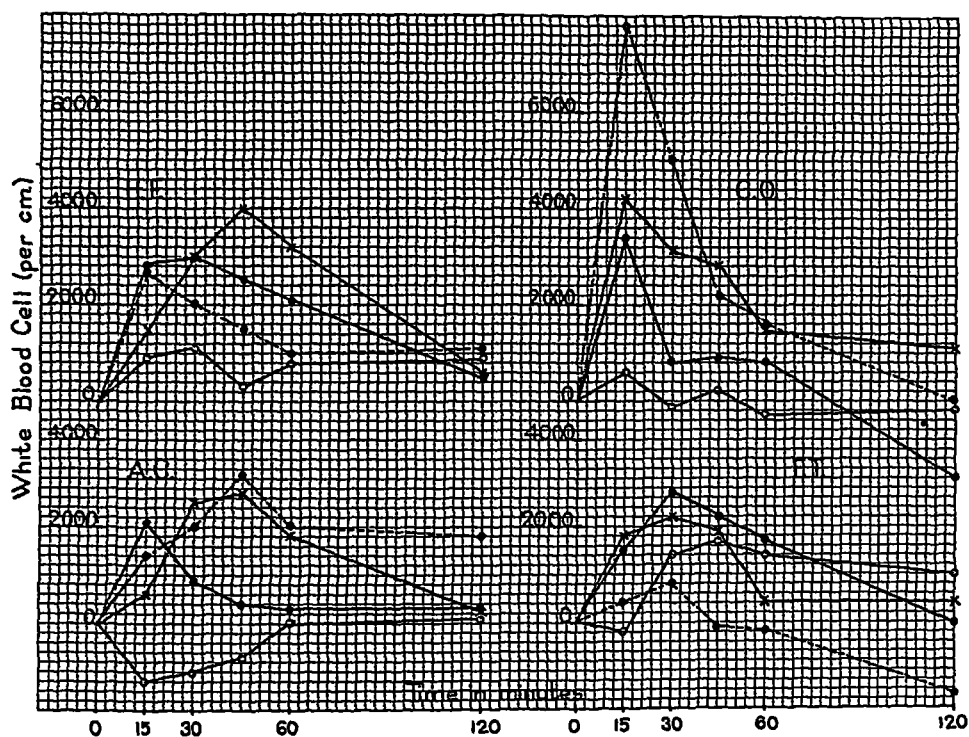


FIG 3 The effect of ergotamine (0.5 mg subcutaneously) on the leukocytosis caused by an injection of epinephrine. In this figure the differences between the initial values and those found after injection are plotted rather than the actual counts, the initial count in each case being taken as zero. The crosses represent experiments in which epinephrine alone, the circles experiments in which ergotamine alone, was given. The solid dots with a solid line represent experiments in which epinephrine was given before the ergotamine, the solid dots and broken lines those in which ergotamine was injected before the epinephrine. The time refers to the intervals after the injection. When both drugs were given it refers to the intervals after the injection of epinephrine. When epinephrine was injected first the ergotamine was given immediately afterwards. When ergotamine was given first, a period of 10 to 15 minutes elapsed before the injection of epinephrine.

With respect to the pulse rate, the pulse slowing action of ergotamine is opposed to the tachycardia caused by epinephrine and the effect of the injection of the two drugs depends on the balance between these two opposing actions. Most, if not all, of the ergotamine effect is, we believe, the result of a stimulation of the vagus and not a depression of the sympathetic. The preponderance of the sympathetic stimulation by epinephrine agrees well with the preponderance of the sympathetics of the heart under normal conditions, and explains the failure of ergotamine to cause any significant inhibition of the tachycardia caused by epinephrine. Whether any of the slight effect of ergotamine is the result of a depression of the sympathetic is diffi-

cult to determine. However, for reasons discussed below it is possible that ergotamine may possess such an action to a slight extent.

The influence of ergotamine on the leukocytosis caused by epinephrine was so irregular that no constant inhibitory action can be attributed to it. It should be noted, however, that in all these experiments the dose of epinephrine was only 0.5 mg.

When the experiments in which 0.5 mg of epinephrine was given are compared with those in which 1.0 mg was used the results are the opposite of those which would be expected, the ergotamine inhibiting the actions of 0.5 mg less than it inhibited the action of double this amount of epinephrine. This offers some support for the theory that ergotamine is able to inhibit the motor sympathetics only when the latter are stimulated and even then (with the doses used) only partially and at the higher levels of stimulation. It may be significant that the greatest effect of ergotamine was observed in the experiments on the metabolic rate and the blood sugar. Both are functions which, as we have shown, are not influenced significantly by ergotamine under basal conditions. Both functions are probably inactive under basal conditions but are susceptible to relatively great and rapid stimulation with epinephrine. Further support for this conception of the mode of action of ergotamine is found in the studies of Wilder.⁹ This author has shown that the actions of certain drugs on the autonomic nervous system exhibit quantitative and qualitative differences which are related to the level of activity of the functions studied (the pulse rate and blood pressure in particular). The greater the activity the less susceptible are these functions to stimulating influences and the more sensitive to depressants, the less the activity the more affected by stimulation and the more resistant to inhibition. This general reaction, according to the author, constitutes a biologic law to which he has applied the term "law of the initial value" ("Ausgangswertgesetz"). Such a "law" is in conformity with the results of this and our previous studies. It will explain the many conflicting reports of the action of ergotamine in clinical experiments. If, to the factor of "stimulation level" one adds the necessity of employing small doses of ergotamine, the partial and irregular inhibition found in man seems more understandable. It is possible also that variations in the rate of absorption of the epinephrine and ergotamine may contribute to the irregularities in experiments such as these.

SUMMARY

Ergotamine, in doses of 0.5 mg given subcutaneously, inhibited partially the increase in metabolic rate and the hyperglycemia which an injection of 1 mg of epinephrine caused in normal subjects. The effect was somewhat greater and more constant when the ergotamine was given after the injection of epinephrine. When 0.5 mg of epinephrine was given, ergotamine had little or no effect. The injection of ergotamine and epinephrine caused a greater increase in blood pressure than resulted from an injection of epi-

nephrine alone The maximum pulse rate was slightly less when both ergotamine and epinephrine were given than when only epinephrine was injected Ergotamine had no constant effect on the increase in the total leukocyte count which occurs following an injection of 0.5 mg of epinephrine Evidence is given for the belief that in man ergotamine is able to depress significantly certain functions of the sympathetic only when the latter are stimulated and that this depressing effect is directly proportional to the degree of sympathetic stimulation

BIBLIOGRAPHY

- 1 YOUNG, J. B., TRIMBLE, W. H., and FRANK, H. Experimental and clinical studies of ergotamine. IV. The effect of ergotamine on basal metabolism, circulation and blood sugar of normal persons and of patients with thyrotoxicosis, *Arch. Int. Med.*, 1931, **xlvii**, 612-632
- 2 CANNON, W. B. Organization for physiological homeostasis, *Physiol. Rev.*, 1929, **ix**, 399-431
- 3 FOLIN, O. K. Laboratory manual of biological chemistry with supplement, 1925, D. Appleton and Company, New York, p. 308
- 4 DALE, H. H. On some physiological actions of ergot, *Jr. Physiol.*, 1906, **xxxiv**, 163-206
- 5 GOLDMAN, M., JR. Recherches cliniques sur l'action de l'ergotamine sur le système végétatif, *Arch. d. mal. du cœur*, 1928, **xxi**, 204-209
- 6 MORETTI, H. L'action hypoglycémisante de l'ergotamine dans le diabète, *Compt. rend. Soc. de biol.*, 1927, **xcvii**, 320-324
- 7 COELHO, E., and DE OLIVEIRA, J. C. Influence de l'ergotamine sur l'hyperglycémie alimentaire chez les sujets normaux et chez les diabétiques, *Compt. rend. Soc. de biol.*, 1928, **xcix**, 1527-1530
- 8 YOUNG, J. B., and TRIMBLE, W. H. Experimental and clinical studies of ergotamine. I. Effect of ergotamine on blood sugar and epinephrine hyperglycemia in trained unanesthetized dogs, *Jr. Pharmacol. and Exper. Therap.*, 1930, **xxxviii**, 121-132
- 9 WILDER, J. Ein unbeachtetes biologisches Gesetz, seine Bedeutung für Forschung und Praxis, *Wien. klin. Wchnschr.*, 1931, **xliv**, 1299-1304

PSYCHIATRIC INVESTIGATION IN INTERNAL MEDICINE *

By MARIE L. CARNS, M D , and ANNETTE C. WASHBURNE, M D ,
Madison, Wisconsin

THERE is nothing novel in the idea that adequate medical care cannot be given to a patient unless his mental and emotional difficulties are understood. However, it seems to us that at present little of a concrete nature is being done in many medical departments in this country to apply this idea. The usual routine consists of a thorough study of the patient for the purpose of ruling out any organic pathology, and this being satisfactorily accomplished, he is discharged with only some such diagnosis as neurasthenia, and possibly a prescription for a sedative. Medical responsibility has seemed too often to end with the establishment of a diagnosis of a functional nervous disorder. We feel that these patients should be studied in a practical manner by a psychiatrist and assisted in the solution of basic problems. We shall briefly outline a few of these case histories and trace the subsequent course of the patient under psychiatric investigation.

CASE I

Mrs. G. S., aged 27 years, was referred to the medical service of the Wisconsin General Hospital on October 26, 1932, with a note from her physician stating "Diagnosis obscure. Roentgen-ray might throw light on condition." Her chief complaint was vomiting. She dated the onset six months before admission, and stated that the vomiting took place shortly after eating. Although it did not occur after every meal at the onset, in the last few months it had become more frequent until by the time of admission there was only an occasional meal which was not followed by emesis. She denied nausea or epigastric pain and stated that her appetite was very good. The emesis was not affected by the type of food ingested. She had lost 20 pounds in weight since the onset of her difficulty. Physical examination showed the patient to be well built but somewhat undernourished. There were no significant abnormalities present. The clinical impression was neurotic vomiting. Routine laboratory studies including a gastric analysis showed no significant deviations from normal. The gastrointestinal series showed no abnormalities of the stomach or duodenal bulb. A barium enema showed some narrowing and poor filling of the sigmoid and terminal ileum, interpreted as probably the result of adhesions (patient had had an appendectomy and partial oophorectomy in 1927). Soft diet, tincture of belladonna minimis 10 before meals, together with sedatives and reassurance that no organic pathology existed, all entirely failed to affect the persistent vomiting.

The patient was transferred to the Neuro-Psychiatric Department on November 7, 1932. A preliminary conversation failed to reveal anything except an unhappy marriage. The patient appeared very unstable. She was distinctly tense, could not sit quietly, was evidently embarrassed and unwilling to go into details on the subject of her marriage. To facilitate matters 6 cc (grs. 4) of sodium amytal were administered intravenously. The patient became mildly exhilarated, all hesitancy and

* Received for publication April 18, 1933.

From the Departments of Medicine and Neuro-Psychiatry, Wisconsin General Hospital, Madison, Wisconsin.

embarrassment disappeared and she gave the following history rapidly and with evident relief. Her childhood had been uneventful, during her school days she had entertained the idea that she might become a nurse but abandoned it because she was 'easily upset by things'. Shortly after leaving high school, she fell in love with and married her present husband. All went well until the birth of the first child. At this time the husband came home drunk and vomited in her presence. This resulted in the first of a long series of quarrels. Intercourse, which up to this time had been pleasing to the patient, now became definitely distasteful and she was conscious of vague pelvic pain. Her physician recommended oophorectomy and salpingectomy. At the time of the operation, the physician said to her "Of course you realize the seriousness of this operation, it will not only affect you physically, but in other ways as well." The postoperative course was physically uneventful, but the tactless warning of the doctor upset the patient emotionally. She entertained fears that she would be crippled sexually, or that she would be "different from other women." Returning home, she began pleading various excuses to escape intercourse, 'backache—the operation,' etc. On one occasion she was forced to use physical resistance.

Six months after the operation she went with her children on a visit to her grandfather, who was in poor health. This was made the excuse, in reality she was fleeing from her husband's attentions. Her last advice to him was, "Go out with other women, if you get a venereal disease that's the price you pay." After a short time the husband suddenly appeared and demanded that the patient return home with him. At this time the vomiting began. At first it occurred just after the evening meal. "He took no notice at first, then he got mad." All attempts at coitus precipitated further emesis. Gradually the periods of vomiting increased and the patient was unable to retain any meal.

Following this conference, the patient appeared less nervous, but the vomiting continued. Psychotherapy was instituted with suggestions as to a connection between the emesis and the sexual conflict, but it was left to the patient to draw the final conclusions. This she did six days later. At this time the vomiting suddenly ceased. The patient was kept in the hospital for four weeks longer without any recurrence of symptoms. Her future was then frankly discussed. Because of the children she was unwilling to contemplate divorce. Having conquered the emesis, she now felt that with a better understanding of her problem she could find readjustment in her marital life. Before her discharge, the situation with obvious reservations was discussed with the husband. A letter received February 15, 1933, from the patient stated that she had gained 15 pounds and was not vomiting at all.

Impression: Situational neurosis with accompanying cotitophobia.

CASE II

Mrs. I. L., a housewife 28 years of age, was first seen by one of us in the medical out-patient department on April 21, 1932. Her chief complaint was "nervousness." She had had an almost continuous series of nasal colds with persistent cough during the past winter. She felt unduly fatigued. Her weight was exactly the same as two years before. At this interview the greatest emphasis was concentrated on the social history. The patient had had four children in a little over four years, the eldest being nine years old and the youngest four and a half years. Her husband had lost his job and she worked six and a half hours daily as an elevator operator. In addition she had household work and other domestic responsibilities to assume. One or more of the children had been ill almost all winter. On questioning she admitted that the husband drank intermittently, came home drunk and was very abusive. However, she gave the impression of great loyalty to him and did not volunteer complaints. She stated that she was not prone to worry about herself and would not have come into

the clinic now unless urged to do so by the visiting nurse, who wished her to be reexamined because of a previously diagnosed pulmonary tuberculosis.

The past medical history is of special interest in this case and will be given in some detail. She was first admitted to the hospital on September 24, 1928 and at that time also her chief complaint was "nervousness," which she then stated was of three years' duration. Other symptoms included easy excitability, palpitation, precordial pain, dyspnea on exertion, considerable muscular weakness and occasional syncope. About four months before this hospital admission, following a weight loss of 30 pounds in a few months, she had attended a chest clinic where she had been diagnosed as having pulmonary tuberculosis and had been sent to a tuberculosis sanatorium. She had remained there up to the time of the hospital admission, having been referred from the sanatorium to the hospital to have her "goiter" treated. She had gained 15 pounds in the four months at the sanatorium and also had regained a good appetite. The social history in the hospital record of this admission stated only "Married six years. Husband living. Housework, busy with four children." The family history was of interest in that both father and mother died of pulmonary tuberculosis during the patient's childhood and there had been intimate contact. The significant findings on physical examination at this time were restlessness, moderate bilateral enlargement of the thyroid, the gland being soft and smooth, rapid pulse, blood pressure 150/90, tremor, hyperreflexia, moist palms and soles, no eye signs of hyperthyroidism, and no quadriceps weakness. Her basal metabolic rate was $+32$ and $+35$. On bed rest, mild sedatives and Lugol's solution minims 5 three times a day for four days the BMR dropped to $+10$ and $+11$. The clinical impression was hyperthyroidism (exophthalmic goiter), and subtotal thyroidectomy was performed on October 26, 1928. The postoperative course was uneventful and the BMR on October 15, 1928 was $+10$ and $+4$. The pathological report of the excised gland was colloid goiter. Stereoscopic roentgen-ray of the chest on September 25, 1928 was read as follows: "Apices relatively clear. Hilum lymph nodes show moderate increase. Several calcified nodules on either side. Calcified plaque anteriorly behind sternal end of fourth rib. Domes of diaphragm round and regular." This was interpreted as showing no evidence at all of recent parenchymal pathology.

She was readmitted on January 23, 1930. At this time her complaints were practically identical with those on her first admission. The physical findings also coincided very closely. The BMR ranged from $+17$ to -1 . She was diagnosed as neurocirculatory asthenia and discharged with a recommendation for sedative medication.

This past medical history now leads up to the findings at the time of the examination cited at the beginning of this case report. The physical findings were in all respects similar to those previously reported. The extreme nervousness was obvious, the patient moving and twisting her hands continuously. The pulse rate was 106. There was a distinct tremor of the hands and evidence of marked vasomotor instability of the skin. The blood pressure was 146/96. It was questioned at this time if the patient had had recent active pulmonary tuberculosis or Graves' disease. It was believed that a situational neurosis superimposed on an unstable autonomic nervous system was the primary condition. In view of this she was referred to a psychiatric consultant. The point of interest in this case is the inference that if a careful social history had been elicited the patient might have been saved from sanatorium treatment for suspected tuberculosis and from thyroidectomy.

The patient was first seen in the psychiatric out-patient department on June 15, 1932. She presented a picture of extreme instability, the cheeks were flushed, the heart rate 106, and there was almost constant wringing of the hands. With considerable encouragement she was finally encouraged to discuss her problem. The husband of the patient was addicted to alcohol. While admitting his lapses, the patient's attitude toward him was highly detached. Her only condemnation lay in the

effect on the children. He would come home drunk and wake them up, frightening them "into tantrums by his carryings on." Her attempts at interference had resulted in physical violence to herself. The patient appeared at her wits' end to know what to do. The conflict resulting between affection for her husband and despair over his actions had now reached an acute stage. She could see no future and appeared overwhelmed by the futility of her life. Practical suggestions such as six months' hospitalization of the husband for alcoholism, legal aid, etc., fell on deaf ears because the patient's affection and fear of her husband would not permit her to consider such measures. She was assured that only when the domestic difficulties were solved would there be an improvement in her own condition.

She was next seen in December 1932. At this time her condition appeared only slightly improved. Though still refusing to take any definite steps in the matter of her husband, she had become convinced of the connection between the home situation and her own nervousness. On March 1, 1933, the patient was again seen in the outpatient department. At this time a definite improvement was noted. She was more composed, sat quietly and was able to discuss her problem without the tremulousness previously noted. The husband had not been drinking for a period of two weeks. Symptoms of increased tension were elicited only when she conversed about the past. The patient left with the assurance that at any time, if the situation became too difficult, she should feel free to summon help.

Impression: Situational neurosis

CASE III

Miss D. C., 23 years of age, was referred to the Wisconsin General Hospital on October 17, 1932, with a diagnosis of "tuberculosis of the left lung with pleurisy, or cardiac trouble." Her chief complaint was pain in the left chest. She dated the onset to about four years before. The pain had been intermittent in character, at times accompanied by a cough which was occasionally productive. She also complained of fatigue, attacks of vertigo associated with scotomata, tinnitus, dyspnea on sudden exertion, palpitation, anorexia, recent syncope and a weight loss of 16 pounds in the past three years.

Examination showed a moderately well developed and well nourished young woman. She was quite uncooperative, jerked and quivered frequently and refused certain parts of the examination. There were no physical findings interpreted as significant. The clinical impression was anxiety neurosis. Routine laboratory examinations showed no significant abnormalities. Sputum examinations were reported as negative for tubercle bacilli on four occasions. The basal metabolic rate was -1 . Stereoscopic roentgen-ray of the chest showed no evidence of recent parenchymal pathology in the lungs. The sinuses were clear. Physiotherapy in the form of radiant heat and light to the left chest, high caloric diet and reassurance that no serious organic pathology was present resulted in no appreciable alleviation of the patient's symptoms.

On November 11, 1932 the patient was seen in psychiatric consultation. She appeared sullen, antagonistic and was unwilling to discuss her problem. To all inquiries, the invariable answers were "I don't care" or "I don't want to talk about it." Questions as to why she had come to the hospital elicited merely a curt recitation of vague pains in the cardiac region.

On being transferred to the Neuro-Psychiatric Department for observation, the patient immediately went to bed and for several days refused to get up or talk at all. On November 21, 1932, 6 cc of sodium amytal (grs 4) were administered intravenously. Almost at once the patient became loquacious. She talked not only freely but with evident relief at being able to express herself. The history obtained at this time may be briefly summarized. Until 1928 she had been entirely well. At this time the other students in school began calling her "bastard" and making fun of her

Many of her friends refused to go with her and when she asked for a reason was told, "If you don't know you ought to be ashamed." Two years of this type of persecution resulted in an attitude of suspicion and depression. In 1930 she was driven to the point of questioning her mother and was told it was true that she was illegitimate. Confirmation of her fears caused the patient to shun society. She became conscious of real or imaginary comments of the neighbors. The attitude of antagonism developed rapidly as the patient became more self centered and introspective. On eliciting the above, suggestive psychotherapy was instituted. The situation was outlined to the patient and rationalized with her. On November 26, 1932 a second intravenous injection of sodium amytal (grs 7) was given and the psychotherapeutic suggestions continued.

Following this treatment improvement was observed. She became more talkative, cooperative, and distinctly approachable. Further conferences (without sodium amytal) seemed to stimulate outside interests and resulted in the making of a number of creditable articles by the patient in the occupational therapy department. At the time of discharge, December 22, 1932, the patient appeared to be satisfactorily adjusted. It is interesting to note that the chest symptoms which began in 1928 corresponded to the onset of the emotional disturbance.

Impression Anxiety neurosis

The above examples selected from a large group illustrate the importance of the social history and the need of psychiatric investigation in certain medical cases. We feel that unless the patient's problem is considered from a psychiatric as well as a physical viewpoint, the examination is of necessity incomplete and frequently the results are disappointing. The use of sodium amytal in psychiatric study has been discussed in previous reports. Its use in abnormal mental conditions was reported by Bleckwenn¹ in 1929. As a valuable aid in analysis it has been used by Lorenz² and his associates since 1930. The technic of administration is simple, and consists of dissolving 1 gram of the preparation in 20 c c of distilled water. The clear fluid is then injected under aseptic conditions into the vein at the rate of 1 c c a minute. After the patient has received 2 to 8 c c, he enters a stage of "excitement" or "talkativeness." At this point the injection is stopped and the analysis begun. It is our impression that sodium amytal is of value because, (1) it permits a rapid and thorough examination with (2) the minimal amount of embarrassment to the patient, and (3) suggestive therapy under this drug is more easily given and more readily absorbed.

SUMMARY

Three cases originally admitted to the medical service are reviewed. In each instance a definite social problem was present. These problems when submitted to psychiatric investigation resulted in improvement of the patient's condition.

REFERENCES

1. BLECKWENN, W. J. Production of sleep and rest in psychotic cases, *Arch. Neurol. and Psychiat.*, 1929, xvi, 365-372—Narcosis as therapy in neuropsychiatric conditions, *Jr. of Med. Assoc.*, 1930, xvi, 1168-1171—Sodium amytal in certain nervous and mental conditions, *Wisconsin Med. Jr.*, 1930, xvi, 693-696.
2. LORENZ, W. F. Criminal confessions under narcosis, *Wisconsin Med. Jr.*, 1932, xxi, 245-250.

EDITORIAL

FEDERAL MEDICAL CARE OF THE UNEMPLOYED

THE PROFESSIONAL medical care of the indigent in the home and in the hospital has heretofore been almost entirely a burden borne by the medical profession unaided. Private philanthropy and public tax money have provided for the construction and operation of hospitals in which the institutional type of medical service could be rendered. The same sources have provided salaries for the pharmacists, nurses, social service workers, technicians, and laboratory physicians working in these institutions. There are, however, comparatively few practicing physicians, if we exclude the physicians of the state and city insane hospitals and tuberculosis sanatoria, who receive salaries for the professional care of indigent patients. The enormous amount of free work done by practicing physicians in the home, in office practice, in the out-patient departments, and on the hospital wards has been the chief burden and at the same time the chief pride of the medical profession. If the value of this free work could be estimated in monetary terms, it would certainly be found to constitute a very large fraction of the total cost of medical service to the indigent.

This present status under which so high a proportion of the true cost of medical care of the indigent is contributed by the physicians in the form of free professional service, is not a satisfactory solution of the problem. It has proved impossible for the profession to furnish adequate medical care to all who are in need. It is true that in many hospitals and in some out-patient clinics, as well as in much of the work done in offices and homes, the free patient has received the highest type of medical care. It can scarcely be denied, however, that it has often proved impossible for the medical profession, especially in these days of depression, to meet adequately all the demands for free work. It is to their credit that they have covered the field as well as they have, and that few indeed of the needy have failed to receive some measure of free medical care.

If the present status may be considered unsatisfactory from the point of view of the inavailability of adequate medical care for a portion of our large indigent population, it must also be considered equally unsatisfactory from the point of view of the medical profession. In a time of shrinkage in their income-producing practice they have felt themselves obliged to carry the burden of an ever increasing number of free patients who were an expense to them not only in time and effort but in actual cash outlay for transportation and medical supplies. Both lay and professional opinion has increasingly favored the view that the cost of the professional care of the indigent should be borne by the community at large. However, since the assumption of this responsibility by any division of the Government would of necessity entail some form of "State Medicine" on a large scale a considerable section

of the medical profession, which for the most part has accepted the principle, has nevertheless been opposed to any of the plans suggested for putting this principle into effect

This Gordian knot has been swiftly cut by the Federal Emergency Relief Administration. The conception of their plan may be traced to the statement in Rule No 1, Section B, which was promulgated on June 23, 1933

"Grants made to the States from Federal funds under the Federal Emergency Relief Act of 1933 may be used for the payment of medical attendance and medical supplies for those families that are receiving relief"

After a brief period of gestation in the summer, the full plan has been delivered to the waiting public towards the end of September in the pamphlet entitled "Rules and Regulations, No 7, Governing Medical Care Provided in the Home to Recipients of Employment Relief". By the time this editorial is published, a form of State Medicine affecting a number of millions of our citizens will be in effect throughout our country

Because of the historical importance of this alteration in the conditions of the practice of medicine, and because it will affect to some extent all physicians and all medical institutions, the complete pamphlet is reprinted in the pages of this journal *

The Federal Emergency Relief Administration purposes, subject to definite conditions, paying the practicing physician a fee for his medical services to the indigent. Similarly it will pay for emergency dentistry, for nursing, and for medical supplies. It will not pay physicians or institutions for medical treatment of the indigent rendered in hospitals or out-patient departments. The Federal Emergency Relief Administration defines the broad lines of policy and procedure, the State and local relief administrations are to formulate the local programs. Representatives of the organized medical, dental, nursing, and pharmaceutical professions, appointed by these professions, are to act in an advisory capacity to the State and local relief administrations in the formulation and adoption of the local programs, and in settling disputed problems. The individual physician retains his freedom to participate or not in the local program for his community, but if he desires to participate he must signify his willingness "to accept the regulations and restrictions inherent in such a program"

These "regulations and restrictions" will be finally defined in the local programs, but it is specified under the heading of procedure that the following requirements must be met. The physician must obtain a written authorization from the local relief officer before treating the patient, he must certify to the relief officer when he considers nursing care is desirable; he must present to the relief officer a written request for such drugs as he deems the patient needs, he must certify that delivery in the home is safe in each instance in which he undertakes to deliver a woman in the home, he must obtain a renewal of authorization whenever an acute illness lasts longer than

* Reprinted from the pamphlet of the Federal Emergency Relief Administration

two weeks or requires more than ten visits or when a chronic illness is protracted beyond two or three months, he must submit monthly bills with specified data, the visits arranged in chronological order, the proper authorizations appended, etc., and finally he must accept a fixed fee schedule which "shall be established on the basis of an appreciable reduction from the prevailing minimum charges for similar services"

The rules and regulations promulgated by the Federal Emergency Relief Administration show evidence of careful preliminary study of the problem and of a wish to accomplish the desired purpose with the least disturbance possible of the normal relations between physicians and patients. Yet it is evident that they leave some important practical questions undecided and that the justice of some of the positions taken may well be questioned. Among the first in importance of the omissions is the lack of a clear cut statement as to whether the indigent patient is to be required to choose his own physician or whether, in the case where he has none, the relief officer will select one for him. The latter alternative would constitute a long step in the direction of a governmental medical service. It will seem to many also that exclusion of hospitals and their physicians and of out-patient departments and their physicians from the benefits of the act is arbitrary and unjust. The majority of these institutions are incurring deficits in their attempt to provide treatment for an increasing number of indigent patients. Their physicians are called upon to give without recompense even more of their time to the care of the indigent than in more prosperous years. It may well be, however, that the new order of things will lead to a larger number of the indigent receiving care in their homes or in doctors' offices, and that thus the clinics and hospitals will indirectly receive economic help by a lightening of their load. The level of medical care for the patients affected will be maintained in these circumstances only if the physician in outside practice clearly distinguishes between those cases which do and those which do not require the facilities of a clinic for their adequate care. It is apparent that time will be required to disclose the advantages and disadvantages of the plan, and that new rulings may alter many of its features.

Our Government in these stirring days is manifestly proceeding upon the assumption that a state of emergency exists which warrants the extension of governmental action into many fields not previously included in its scope. The physician now falls into the company of the merchant, the manufacturer and the laboring man as one whose occupation is to some extent altered in its conditions by Federal decree. It must be pointed out that in the physician's case the change is a relatively minor one and that he has been left so far with entire liberty of action.

The people of this country have shown plainly their disposition to accept in good spirit the radical actions of the Government and, whether individually doubtful of the results or not, to use every effort to give to the new measures every chance for success. The medical profession should do no less. It should accept these rulings establishing a form of State medicine as

temporary and emergency measures and give its best efforts to the task of accomplishing their purpose, "the provision of good medical service at low cost—to the mutual benefit of indigent patient, physician, nurse, dentist and tax-payer"

RULES AND REGULATIONS

No 7

GOVERNING MEDICAL CARE PROVIDED IN THE HOME TO RECIPIENTS OF UNEMPLOYMENT RELIEF

INTRODUCTION

The conservation and maintenance of the public health is a primary function of our Government. In this emergency, the ingenuity of Federal, State, and local relief officials is being taxed to conserve available public funds and, at the same time, to give adequate relief to those in need. To assist State and local relief administrations in the achievement of these aims, with regard to medical care, two steps have been taken. First, to define the general scope of authorized medical care, where the expenditure of Federal Emergency Relief Funds is involved, and second, to establish general regulations governing the provision of such medical care to recipients of unemployment relief.

GENERAL SCOPE

(Extracted from rules nos 1 and 3, previously established)

Promulgated on June 23, 1933, rule no 1, section (b), stated

Grants made to the States from Federal funds under the Federal Emergency Relief Act of 1933 may be used for the payment of medical attendance and medical supplies for those families that are receiving relief.

The permission granted under this section (b) was more sharply defined in the same rule in section (d), which stated in part

These funds may not be used for the payment of hospital bills, or for providing general institutional care. These necessary services to the destitute should be made available through State or local funds.

In the section on "Direct Relief" of rule no 3, promulgated on July 15, 1933, medical care in the home was listed as item 6 in the list of the types of relief that may be provided to relief cases, viz:

"To Order for medicine, medical supplies and/or medical attendance to be furnished in the home. Under the same rule adequacy of such relief is made "an obligation on the State Emergency Relief Administration and on all the political subdivisions of the States to furnish relief."

The term of medical care as above defined shall be construed to include Bed-room nursing care as an adjunct to medical care, and emergency dental service for persons receiving relief.

REGULATIONS GOVERNING MEDICAL CARE PROVIDED IN THE HOME TO RECIPIENTS OF UNEMPLOYMENT RELIEF

The following regulation, governing the provision in the home of medical care (including medical supplies and/or medical attendance) to persons eligible for unemployment relief, was hereby established:

1 *Policy* A uniform policy with regard to the provision of medical, nursing, and dental care for indigent persons in their homes, shall be made the basis of an agreement between the relief administration and the organized medical, nursing, and dental professions, State and/or local. The essence of such a policy should be

(a) An agreement by the relief administration to recognize within legal and economic limitations, the traditional family and family-physician relationship in the authorization of medical care for indigent persons in their homes, the traditional physician-nurse relationship in the authorization of bed-side nursing care, the traditional dentist-patient relationship in the authorization of emergency dental care, and

(b) An agreement by the physician, nurse (or nursing organization), and dentist to furnish the same type of service to an indigent person as would be rendered to a private patient, but that such authorized service shall be a minimum consistent with good professional judgment, and shall be charged for at an agreed rate which makes due allowance for the conservation of relief funds

The common aim should be the provision of good medical service at a low cost—to the mutual benefit of indigent patient, physician, nurse, dentist, and taxpayer

The policy adopted shall be to augment and render more adequate facilities already existing in the community for the provision of medical care by the medical, nursing, and dental professions to indigent persons. It shall imply continuance in the use of hospitals, clinics, and medical, dental, and nursing services already established in the community and paid for, in whole or in part, from local and/or State funds in accordance with local statutes or charter provisions. Federal Emergency Relief Funds shall not be used in lieu of local and/or State funds to pay for these established services

The phrase "in their homes" shall be interpreted to include office service for ambulatory patients, with the understanding that such office service shall not supplant the services of clinics already provided in the community

2 *Procedure* A uniform procedure for authorization of medical, nursing, and dental care in the home shall be established by each State and/or local emergency relief administration. This procedure shall not be in conflict with the following requirements

(a) *Written Order* All authorizations for medical, nursing, and dental care shall be issued in writing by the local relief officer, on the regular relief order blank, prior to giving such care, except that telephone authorization shall immediately be followed by such a written order, and provided that authorizations for bed-side nursing care shall be based on a recommendation by the attending physician, in cases where a physician is in attendance, who shall certify to the need for nursing service as part of the medical care. Authorizations for medicine and medical supplies shall also be issued in writing and, in general, such authorizations shall not be issued except upon written request of the physician authorized to attend the person for whose use they are desired

(b) *Acute Illness* Authorizations for medical care for acute illness shall be limited to a definite period and a maximum expenditure or number of visits (i.e., not more than 2 weeks or 10 visits), according to the standard agreement made between relief officials and physicians under regulation 1. Medical care in excess of this period shall not be authorized until after a reinvestigation of the case in the home by the local emergency relief administration

(c) *Chronic Illness* Medical care for prolonged illnesses, such as chronic asthma, chronic heart disease, chronic rheumatism, diabetes, etc., shall be authorized on an individual basis, and, in general, visits shall be limited in frequency (i.e., not more than 1 visit per week for a period not exceeding 2 or 3 months) by agreement. Nursing care for such chronic illnesses shall, in general, be authorized in accordance with the need for such care as indicated by the attending physician. If necessary, more frequent visits, by the physician or nurse, for an acute attack occurring in the course

of a chronic illness, may be authorized. Care for chronic illness authorized under this section shall supplement and not supersede existing community services, such as visiting nursing service or institutional care.

(d) *Obstetrical Care* Authorization for obstetrical service in the home shall include an agreed minimum number of prenatal visits (where possible), delivery in the home, and necessary postnatal care. Due caution shall be exercised that this authorization for delivery in the home does not involve undue risk to the patient for whom hospital care may be imperative. The physician authorized to attend the confinement in the home shall be responsible for certifying to the local relief administration that, in his professional judgment, delivery in the home will be safe.

(e) *Special Services* Medical and nursing services not covered above shall be authorized on an individual basis, subject to the general provisions of the agreement made under regulation 1. Special dental service shall be subject to a similar procedure.

Medical care shall not ordinarily be authorized by relief administrations for conditions that do not cause acute suffering, interfere with earning capacity, endanger life, or threaten some permanent new handicap that is preventable when medical care is sought.

(f) *Accessory Services* Emergency dental care and bedside nursing service, for indigent persons in their homes, may be authorized subject to the existing general policy of the State and/or local relief administration.

(1) *Dental care* shall, in general, be restricted to emergency extractions and repairs. Dentists and dental care shall be subject to the same general restrictions indicated for physicians under regulation 1.

(2) *Bedside nursing care*, where authorized, shall conform to a procedure comparable to the one outlined for physicians above, and shall be provided under an agreement made between relief administrations and nursing organizations, State and/or local, under the same principles suggested for physicians under regulation 1. Standards of accredited local nursing organizations shall be followed by nurses giving authorized bedside nursing care to indigent persons in their homes. Such authorized bedside nursing care shall not supersede or supplant existing local official services giving such care under the provisions of local law.

(g) *Fee Schedule.* The agreement between the State and/or local relief administration and the organized professional groups of physicians, nurses, and dentists, State and/or local, established under regulation 1, shall include a fee schedule covering the basic and special services outlined in sections (b) to (f), inclusive, of this regulation. In the interests of simplified accounting it is suggested that a flat rate be established, on a per visit basis for the usual care given to acute and chronic illness (sections (b) and (c) above), for attendance at confinement (section (d) above), for emergency extractions (section (f) above), and for a bedside nursing visit (section (g) above), and that all special services (medical, nursing, or dental) be covered by an agreed reduction from the usual minimum fee schedule for such services with an agreed maximum fee. A recognized differential in fee shall be established between a home and an office visit. All fees shall be established on the basis of an agreed reduction from the prevailing minimum charges for similar services in the State and local communities, with due recognition of the certainty, simplicity and promptness of payment that authorization from the local relief administration insures.

The schedule shall only apply where the expenditure of Federal Relief Funds is involved and shall not preclude the payment of additional amounts from local funds.

Where bedside nursing care is authorized, that rate per visit shall be established as a maximum not to exceed the certified cost per visit established for accredited nursing organizations in the State or local district.

Physicians, nurses (or nursing organizations), and dentists who are authorized to provide care to indigent persons in their homes shall submit

to the local relief official, monthly (within 10 days after the last day of the calendar month in which such medical care was provided), an itemized bill for each patient. Each bill shall be chronologically arranged and shall contain at least enough information to permit proper audit (i.e., name, age, and address of patient, general nature of illness or diagnosis, whether home or office treatment, dates of service, and status of case at end of month—cured, sent to hospital, dead, needs further care, etc.). Bills for medical care shall be accompanied by the original written order for such care, except for cases in which medical service under an authorization has not terminated during the calendar month covered by the bill, in which cases the bill shall show, in addition to the details required above, the date and serial number of the outstanding order. Retroactive authorizations shall not be issued or honored for payment.

Bills for special and accessory services, outlined under sections (e) and (f) above, shall give full details of such services, and bills for medicines and medical supplies, under (1) below, shall be subject to the same general requirements. Bills for drugs shall list the name and quantity of each. The formula and number of each prescription costing more than 25 cents shall be submitted with or made a part of the pharmacist's bill.

NOTE The submission of bills and their audit and authorization for payment will be simplified if the State Emergency Relief Administration provides a suitable bill form.

(1) *Medicine and Medical Supplies* Physicians providing authorized medical care to indigent persons shall use a formulary which excludes expensive drugs where less expensive drugs can be used with the same therapeutic effect. When expensive medication is considered essential by the authorized attending physician it may be authorized after consultation with the local medical advisory committee.

Prescriptions for necessary drugs and medicine shall be restricted to the National Formulary or the United States Pharmacopeia. To avoid excessive expenditures for remedies of unknown or doubtful value proprietary or patent medicines shall not be authorized.

State and/or local relief officials are urged to make trade agreements with pharmaceutical organizations and druggists for uniform or reduced rates for prescriptions.

Authorizations for medical supplies shall be restricted to the simplest emergency needs of the patient consistent with good medical care.

In general, authorizations for medicine and medical supplies shall not be issued except upon written request of the physician authorized to attend the person for whose use they are desired.

3 Authority The State emergency relief administration, responsible for the distribution of Federal and State Emergency Relief Funds to local relief administrations, shall give approval to such statements of policy, proposed fee schedules, and detailed procedures, governing the provision of medical, nursing, and dental care in the home to recipients of unemployment relief, as may be established by State and/or local relief administrations, in accordance with the provisions of regulations 1 and 2, above, before such policies, schedules, and procedures shall take effect. It shall be the responsibility of the State emergency relief administration to formulate a program of medical, nursing, and dental care for indigent persons in their homes, which shall not be in conflict with the provisions of regulations 1 and 2, above, and to make sure, by giving or withholding approval, that analogous programs formulated by local relief administrations shall not be in conflict with such State program.

(a) *State and Local Professional Advisory Committees* State and local relief administrations shall request the presidents of the State and local medical, nursing, dental, and pharmaceutical organizations, respectively, to designate an existing committee or appoint a special committee, to advise them in the formulation and adoption

of adequate programs for medical, nursing, and dental care in the home for indigent persons. The relief administrations shall be responsible for the final adoption of such programs. The medical, nursing, dental, and pharmaceutical advisory committees can assist these administrations in maintaining proper professional standards and in enlisting the cooperation of the constituent, professional membership in such programs. Local medical, nursing, and dental programs submitted to the State relief administration for approval should be submitted to the appropriate professional advisory committee for comment, before final approval is given. The appropriate professional advisory committees should be consulted by relief administrations with regard to disputed problems of medical, nursing, and dental policy and practice.

(b) *Licensed Practitioners of Medicine and Related Professions* When a program of medical care in the home for indigent persons has been officially adopted, participation shall be open to all physicians licensed to practice medicine in the State, subject to local statutory limitations and the general policy outlined in regulation 1, above. Physicians authorized by relief officials to give medical care under this program shall have accepted, or shall be willing to accept, the regulations and restrictions inherent in such a program. In order to provide adequate medical care it may be desirable for local relief officials to maintain on a district basis a list or file of physicians in the community who have agreed in writing to comply with the officially adopted program. Such a list of physicians should also facilitate a more equitable distribution of orders for medical services.

A similar policy and procedure shall be followed in the preparation of approved lists of nurses, dentists, and pharmacists. Licensure and/or registration to practice their respective professions in the State shall be a prerequisite to approval of graduate nurses, dentists, and pharmacists for authorized participation in the officially approved State program for the provision of medical care for indigent persons in their homes.

(c) *State Program for Medical Care to Indigent Persons in Their Homes* When the State emergency relief administration has adopted a uniform program for medical, nursing, and dental care for indigent persons in their homes, in accordance with these rules, a copy of such program, including the statement of policy, fee schedules, and detailed procedures, shall be filed immediately with the Federal Emergency Relief Administration.

REVIEWS

An Index of Treatment By various writers, edited by ROBERT HUTCHINSON, M D, F R C P Tenth Edition, Revised xviii + 1027 pages, 18 × 26 cm William Wood and Company, New York 1931 Price, \$12 00

This, the tenth edition of a work first published in 1907, is suited to the needs of the general practitioner rather than to those of the specialist of any type It includes medicine, surgery gynecology, obstetrics, and practically all other branches in its scope, and of necessity, the treatment of many diseases is outlined in one plan only, rather than allowing several alternatives

The section on diabetes mellitus, by Edmund Speggs, is quite complete Several methods of dietetic treatment are fully outlined, the choice of method depending on the physician and patient Directions for making up menus according to a dietary prescription are much clearer and more easily followed than those in most textbooks High carbohydrate diets are only suggested, and except in the section on diabetes in children, a maximum of 100 gm daily is given Less attention is paid to surgical complications than is desirable The section on the treatment of coma is clear and complete

A special section on the treatment of diabetes in childhood, by George Graham, is included It contains several useful suggestions, and advocates high carbohydrate diets Tables of food composition, by A J Leigh, are rather complete and made up in an unusual and very helpful way, which should facilitate very much the calculation of diets

The English origin of this book is emphasized by the assignment of five times more space to the treatment of gout than is devoted to the medical treatment of duodenal ulcer Only one plan of treatment for duodenal ulcer is suggested The suggestion that operation should be carried out as soon as possible after a hemorrhage is unusual, especially when contrasted to the conservative treatment of hemorrhage usually followed in this country

The section on pneumonia is disappointing Only one method of oxygen administration is suggested, that of the nasal catheter Oxygen tents and chambers are not discussed, nor is the quantity of oxygen given mentioned at all Serum treatment is dismissed in a short paragraph without recommendation even in Type I pneumonias The recommendation of intravenous mercurials in the presence of a positive blood culture is startling

Much useful information about nursing procedures, physiotherapy, and other methods of treatment is given The almost exclusive use of the English system of weights and measures is a disadvantage, as most schools in this country are attempting to adopt the metric system Likewise the frequent mention of English proprietary drugs, without the names of the manufacturers, is confusing Spa treatment is emphasized, the health resorts in the United States are not mentioned The introduction, by the editor, discusses the importance of a well organized plan of treatment, and serves to correlate the main contents of the book

It is inevitable in a work of this type, with so many individual contributors, that some unevenness of value should occur The average is high, however, and throughout the book there is evidence of care in preparation and organization Many articles supplement each other Indexing is complete As a compact and ready source of

therapeutic information for the physician in active practice this book has a distinct field of usefulness

T N C

An Index of Prognosis and End-Results of Treatment. By various writers, edited by A RENDLE SHORT, B S, B Sc (Lond), F R C S (Eng) Fourth Edition, Fully Revised xi + 599 pages, 18 X 26 cm William Wood and Company, New York 1932 Price, \$13 50

This volume is a companion to the *Index of Differential Diagnosis and Index of Treatment*, issued by the same publishers, and follows the same general plan of organization. It includes practically all branches of medicine and surgery. The purposes of the work, as stated in the preface to the first edition and repeated in that of the present edition are

"1 To set forth the results, and particularly the end-results of treatment, in such a form as will enable the practitioner to obtain a fair, unbiased, reasoned opinion as to the prospects of securing for his patient permanent relief, and the risks of such treatment

"2 To furnish data by means of which, apart from the question of treatment, one may arrive at an accurate forecast of what will probably happen to the individual patient"

The book exhibits a degree of uniformity unusual in a composite work of this type. In general, the same plan is carried out in discussion of different diseases. Prognosis as to recovery from acute disease is discussed in general, together with effects of treatment. The incidence of complications and sequelae is outlined fully. In the sections on chronic diseases, prognosis as to ultimate recovery, retention of function, and ultimate duration of life are discussed.

The surgical articles, many of which are contributed by the editor, A Rendle Short, are very interesting. Types of operation, mortality from operative procedures, immediate and late result of operation, with complicating factors, are fully outlined. Tables which can be read at a glance are included in many of the articles. Statistics, as a rule, are recent and carefully analyzed, and a satisfactory bibliography is usually included. Very full discussion is given those diseases which admit of either "medical" or "surgical" treatment. In this class falls the article on peptic ulcer, contributed by the editor.

The sections devoted to medical diseases are, as a rule, less formally written and not so well documented as the surgical articles, with fewer statistical tables, but in spite of this they are none the less interesting and informative. Articles on cardiovascular disease, largely contributed by C F Coombs, C B Perry, and E J Poynton are quite complete. Most of the neurological sections are by J Purves-Stewart.

An especially valuable chapter on anesthetics is contributed by D W Buxton. Anesthetic hazards, effect of anesthesia on disease, incidence of complications from different anesthetics, and the choice of anesthetics for types of patients and operations are fully discussed.

This book should be a valuable addition to any physician's library. The information throughout is clear, accessible and well digested, and presented in a very interesting manner.

T. N. C

Pediatrics By HENRY DWIGHT CHAPIN, M A , M D , Professor Emeritus of Pediatrics, New York Post-Graduate Medical School, Columbia University, and LAWRENCE T ROYSTER, M D , Professor of Pediatrics and Head of the Department of Pediatrics, University of Virginia xvi + 775 pages, 16 X 23 cm William Wood and Co , Baltimore, Maryland 1933 Price, \$7 00

This is the seventh revised and enlarged edition of the standard textbook which was first published in 1910 under the title of *Diseases of Infants and Children*. It is an eminently practical book whose value to the profession is attested by the appearance of repeated new editions.

The first section deals with growth and development and includes a splendid chapter on the appraisal of the child. This is followed by excellent chapters on the feeding of newly born children and infants. The advances of the past five years in the knowledge of digestion and metabolism of food elements are well presented. An entire chapter is devoted to the latest conceptions of the vitamins. New sections on ketosis and alkalis have been added under diseases of the digestive tract.

Intelligence tests are described, as well as various diagnostic and therapeutic procedures. The chapter on diseases of the brain includes a concise discussion of lead poisoning. Another interesting new article is the consideration of erythroblastic anemia which the author placed in the class of primary anemias.

Finally there is a chapter on the care of dependent infants and children which should prove especially interesting to the general practitioner.

The main divisions of the book are based on the systems of the human body, to which are added a section on infectious diseases and one on the commoner surgical diseases. It is pleasing to note that the section on diseases of nutrition is completely separated from that on diseases of the digestive tract.

This book is useful and this new edition will prove valuable alike to pediatricians, practitioners and students.

A H F

Biochemistry of Medicine By A T CAMERON, M A , D Sc , F I C , F R S C , and C R GILMOUR, M D , C M , F R C P (C) 506 pages, 22 5 X 15 cm Wm Wood and Co , Baltimore, Maryland 1933

As the title implies, this book is written for the student of medicine rather than for the student of pure biochemistry. The authors have undertaken successfully to present to those in the medical profession a text which will correlate and interpret biochemical data with reference to their medical significance. There has been no attempt to present pure theoretical biochemistry except where such information would lead to a better understanding of the subject discussed.

The normal metabolism of carbohydrates, fats, and proteins is discussed in sufficient detail to enable the reader to appreciate the complete analyses of abnormalities in these fields. The authors have gone further than a mere statement of diseases and causes for they have given within the text those tests that are essential for the identification of the disease or corroboration of their diagnosis. Clinical symptoms, theoretical interpretations and chemical tests are presented in such a fashion as has rarely been found in a single text. The rare diseases are discussed in as much detail as past and recent investigations permit. The discussion of the abnormalities of protein metabolism is particularly complete.

The chapter headed "Metabolism of Water. Passage of water and dissolved substances across animal membranes. Edema and kidney function" is one of the most able of its kind. A vast subject is covered in a remarkably condensed and com-

plete fashion. The authors have covered the literature up to and including the latest publications. For example the short paragraph on the formation of the cerebrospinal fluid summarizes completely this important physiological process from the chemical viewpoint while the references cover the subject in theoretical and technical details.

Other than this there is a necessarily short discussion on respiration, a chapter on the endocrine secretions and a more or less outlined account on the vitamins, their sources and the functional disturbances caused by their deficiencies. To these have been added short chapters on gastric functional tests and liver tests, giving a short description of those used in most laboratories or those suggested in recent papers.

The authors have added to the value of the book by placing at the end of each chapter a short summary and the latest references which are pertinent to the subject discussed.

Biochemistry of Medicine is an excellent supplementary text for any professional man who wishes to review his biochemistry in terms of the cases he has seen or for the student who wishes to correlate his pure biochemistry with clinical data.

E M R

Der dialektische Materialismus und die klinische Medizin By Professor J LIRSCHTZ (Allukrainische Gesellschaft zur Forderung der kulturellen Verbindungen mit dem Auslande) Paper 80 pages Medwydaw Kharkiw 1932

This small monograph is essentially propaganda, setting forth the ideas and theories of Soviet Republicanism so far as the philosophic view of medicine is concerned. It is of little value, except to show the trend of scientific and philosophic thought as applied to medicine in present day Russia.

A C G

Diet in Sinus Infections and Colds By EGON V ULLMANN 166 pages The Macmillan Company, New York

In the introduction to his book the author states that "this work constitutes the first systematic attempt to apply the modern knowledge of nutrition to individuals who suffer from repeated colds and sinus infections." The attempt has not been wholly successful. The editor, it is true, rather than the author (whose training seems to have been chiefly in Vienna), must be responsible for the retention of foreign expressions, and the German phraseology transferred bodily into English. For example phosphorus is "phosphor," lecithin is "lezithum," and chlorine is "chlor", the adjectives "animalic" and "vegetabilic" occur throughout, and food is continually being "exploited." One chapter is devoted to a condensed and somewhat inaccurate exposition of elemental chemistry, and another to the estimation of urinary acids and urinary chlorides. The author deprecates the ingestion of too much water in the diet. He prefers alkaline foods, and believes in the reduction or the use of animal proteins, as well as of carbohydrates whenever possible. Fruits and preserves should be used only when canned in glass jars. Curtasal should be used instead of salt.

One of the author's most emphasized aversions is to sodium chloride, to the extent of which in the food he ascribes many ills. He states that it may be "the cause of flatulencies, and hence of bad breath which "is quite often due to the accumulation of food in the stomach." He states that the intake of sodium chloride is "the most important factor in the utilization of proteins," and that "the use of sodium chloride—like nicotine, alcohol and opium." "No one was ever cured by the use of sodium chloride." The modern treatment which deprives

patients with high blood pressure and kidney disease of table salt is the best proof that man can get along without it" Finally appears the remarkable statement that "if sodium is 'eliminated in the intake,' the biological effect of calcium will be enforced, and the diet will work antiphlogistically"

The book contains statements such as the following "Plums and prunes have a solvent effect on the catarrhs of the digestive tract" "Blackberries produce perspiration and dissolve mucus" "Sprue can be cured only with a diet of fresh strawberries" "Lemon juice has a caustic effect on the mucous membranes of the stomach, and is decalcifying to the enamel of the teeth, and may even lead to poisoning" "Onions should not be given in kidney diseases" Perhaps the most interesting fact about this book is that it is sponsored by a firm whose reputation in the field of medical publication is very high

G A H

COLLEGE NEWS NOTES

1934 CLINICAL SESSION

The eighteenth Annual Clinical Session of the American College of Physicians will be held in Chicago, April 16-20, 1934, with headquarters at the Palmer House. As President of the College, Dr. George Morris Piersol, Philadelphia, has charge of the preparation of the program of general sessions. Dr. James B. Herrick, Chicago, was appointed General Chairman by the Board of Regents and will have charge of local arrangements. Dr. Herrick has appointed Dr. Arthur R. Elliott, Chicago, as chairman of the committee responsible for the preparation of the program of clinics in various Chicago institutions and hospitals.

APPOINTMENTS TO THE BOARD OF GOVERNORS

In accordance with provisions of the By-Laws of the American College of Physicians, Dr. George Morris Piersol, President, has made the following appointments to the Board of Governors, the appointees to hold office until the next regular election:

- Dr. Clarence L. Andrews, Atlantic City, N. J., to fill vacancy caused by the death of Dr. W. Blair Stewart;
Dr. Robert B. Kerr, Manchester, N. H., to fill vacancy caused by the death of Dr. Edward O. Otis.
-

Acknowledgment is made of the receipt of the following donations to the Library of the American College of Physicians by authors who are members of the College:

- Dr. Randall Clifford (Fellow), Boston, Mass.—1 book "The Sputum: Its Examination and Clinical Significance",
Dr. William D. Reid (Fellow), Boston, Mass.—2 books "Diseases of the Heart" and "Teaching Methods in Medicine",
Dr. Lodovico Mancusi-Ungaro (Fellow), Newark, N. J.—2 reprints,
Dr. Samuel Weiss (Fellow), New York, N. Y.—1 reprint,
Dr. Edgar F. Kiser (Fellow), Indianapolis, Ind.—1 reprint,
Dr. Hillyer Rudisill, Jr. (Fellow), Charleston, S. C.—2 reprints,
Dr. Joseph B. Wolpe (Associate), Philadelphia, Pa.—7 reprints,
Dr. Burton I. Zohman (Associate), Brooklyn, N. Y.—4 reprints.
-

A Committee for Survey of Research on the Gonococcus and Gonococcal Infections has been formed by the Division of Medical Sciences of the National Research Council, in cooperation with the American Social Hygiene Association. Its purpose is to collect, analyze and collate the facts already established and the efforts now in progress to add to knowledge of the gonococcus and gonococcal infections, as to its requirements, bacteriology, pathology, immunity, mechanism of infection and modes of therapy.

Dr. Walter Clarke (Fellow), New York City, is Secretary of the Committee, and Dr. Francis D'Arcy (Fellow), New Haven, Conn., is Chairman of the Division.

Dr Charles R Drake (Fellow), Minneapolis, was recently elected by a large majority School Director of the Minneapolis Public Schools

Dr Marjorie E Reed (Associate), Plymouth, Pa, recently accepted an invitation to become a member of the Editorial Board of the Child Welfare and Public Health Department of the Medical and Professional Woman's Journal

The Extension Division of the University of Oklahoma, in cooperation with the Oklahoma State Medical Association, will offer a series of medical lectures for county medical societies in that State Among lecturers selected to present courses, the following Fellows are included

Dr Lea A Riely,
Dr L J Moorman,
Dr Ray M Balyeat,
Dr A B Chase,
Dr John E Heatley,
Dr Wann Langston,
Dr Everett S Lain,
Dr J T Martin,
Dr E C Mason,
Dr R C Pigford,
Dr H H Turner,
Dr A W White,
Dr C M Pounders

Dr J W Torbett (Fellow), Marlin, Texas, addressed the American Physical Therapy Association, Chicago, September 12, 1933, on "The Recent Advances in the Dietetic Treatment of Chronic Diseases"

Dr Isaac Seth Hirsch (Fellow) has been made Professor of Roentgenology at the New York University and Bellevue Hospital Medical College, succeeding Dr Leon T LeWald (Fellow), who has retired

Dr John I Marker (Fellow), Davenport, Iowa, was recently elected Secretary of the Iowa and Illinois Central District Medical Association

Dr George S Johnson (Associate), formerly Assistant Director of the Colorado Psychopathic Hospital of the University of Colorado, became Professor of Neuro-psychiatry at Stanford University School of Medicine September 1, 1933

Lt Col Harley J Hallett (Fellow), U S Army, has been relieved at Fort Humphreys, Va, and assigned to the Hawaiian Department

Major John G Knauer (Associate), U S Army, has been relieved at Walter Reed General Hospital, Washington, and assigned to Balboa Heights, C Z

Dr Frank N Gordon (Fellow) has been transferred from the U S Veterans' Administration Hospital at Dwight, Ill, to the U S Veterans' Administration Hospital at Dayton, Ohio

Dr Bryan M Riley (Fellow), Omaha, a member of the faculty of the Creighton University School of Medicine for the past thirty-three years, was recently appointed Dean, to succeed the late Dr Herman von W Schulte

Dr Adolph Sachs (Fellow), Omaha, also a member of the faculty for many years, succeeds Dr Riley as Head of the Department of Internal Medicine at Creighton University and St Joseph Hospital

Dr H A Pattison (Fellow), Livingston, N Y, has been appointed by the National Tuberculosis Association as representative on the special After-Care Committee of the International Union Against Tuberculosis

Dr Joel J White (Fellow), Lieut-Commander, Medical Corps, U S Navy, who has been on duty during the past four years in Washington, D C, as a member of the Faculty of the U S Naval Medical School and in charge of the Division of Aviation Medicine, Bureau of Medicine and Surgery, and also as instructor in Aviation Medicine on the Faculty of Georgetown University, School of Medicine, 1932-33 Session, has been detailed to the Staff of Admiral A W Johnson, Commander Aircraft, Base Force, U S Fleet, on the U S S Wright, Flagship, based at San Diego, California

Dr White recently received a Letter of Commendation from the Secretary of the Navy for the development of an instrument for the analysis of the air in the cockpits and cabins of airplanes to determine carbon monoxide concentration Dr White is the author of an article entitled "Carbon Monoxide and Its Relation to Aircraft," which appeared in the April 1932 issue of the *Naval Medical Bulletin*

Dr Howard S Brasted (Fellow), Hornell, N Y, was recently elected Secretary of the Seventh District Branch of the New York State Medical Society

Dr Ralph Pemberton (Fellow), Philadelphia, Pa, Associate Professor of Medicine in the University of Pennsylvania Graduate School of Medicine and Chairman of the American Committee for the Control of Rheumatism, was the guest speaker on the occasion of a Joint Meeting of the Fifth Councilor District of the Illinois State Medical Society and the Sangamon County Medical Society, at Springfield, Ill, on October 5

Dr Louis Fugere, Bishop, Jr (Fellow), New York, N Y, has been appointed Consulting Cardiologist to The John T Mather Memorial Hospital of Port Jefferson, New York

Dr J O Hood (Fellow), Forsyth, Ga, was recently reappointed to the State Board of Medical Examiners for a term of four years, ending September 1, 1937

Dr Edwin R. Ball Jr (Fellow), Charleston, S C, is pursuing postgraduate studies at the National Roentgen Institute, London

Dr J. S. A. Tucker (Fellow), Washington, D C, Chairman, Dr Cary T. Tucker, Washington, D C, Vice Chairman, and Dr. William Gerry

Morgan (Fellow), Washington, D C, Committeeman, were a Committee for the Southern Medical Association's post-meeting visit to Washington, November 18

Dr E S Lain (Fellow), Oklahoma City, Okla, received a Class I award for research on "Electro-Galvanic Lesions of the Oral Cavity Produced by Artificial Dentures" from the American Medical Association

The Association of Life Insurance Medical Directors of America met at Toronto on October 12 Dr Samuel B Scholz, Jr (Associate), Philadelphia, Pa, will act as Editor of the Proceedings The meeting was addressed, among others, by Dr Charles F Martin (Master), Montreal, P Q, Dr Lewellys F Barker (Fellow), Baltimore, Md, Dr Jabez H Elliott (Fellow), Toronto, Ont, and Dr I M Rabinowitch (Fellow), Montreal, P Q

Gas-Gangrene Antitoxin (National)

Therapeutic Use

Gas-Gangrene Antitoxin is especially indicated in the treatment of gas gangrene infection, peritonitis, gangrenous appendicitis, gas phlegmon, chronic ulcers and other perfringens and vibriion septique infections

Immediately symptoms of gas gangrene develop the serum should be slightly warmed and administered intravenously, also into tissues around the wound when possible, and injections made slowly. Additional doses of serum are advised at 8 to 12 hour intervals as indicated by effect of the specific serum treatment

Identification of the anaerobic spore forming bacteria requires much time and involves great technical difficulties. It is therefore necessary to institute treatment promptly with a bi-valent Gas-Gangrene Antitoxin. All foreign material should be removed from the wound.

Gas-Gangrene Antitoxin is standardized in definite units strength and furnished in perfected syringes, with chromium (rustless) steel needles, containing

Perfringens Antitoxin	10,000 units
(Cl. Welchii)	
Vibriion Septique	10,000 "



Prophylactic Use

Tetanus-Perfringens Antitoxin is for prophylactic use against tetanus and gas-gangrene infections. A prophylactic dose contains Tetanus Antitoxin with Perfringens and Vibriion Septique Antitoxins. Furnished in perfected syringes, with chromium (rustless) steel needles, each syringe containing

Tetanus Antitoxin	1500 units
Perfringens Antitoxin	2000 "
Vibriion Septique Antitoxin	2000 "

The contents of the syringe should be injected subcutaneously, or intramuscularly, so soon as possible after the injury. If the wound is slow in healing a second or third injection should be given at intervals of one to two weeks. This is important in compound fractures, gun shot or cartridge wounds and when contaminated wound areas are involved.

THE NATIONAL DRUG COMPANY
PHILADELPHIA
U.S.A.



Mail Brochure on Gas-Gangrene Antitoxin per adv. in Annals of Internal Medicine

Name

Address

State

Date

A Room and a Bath for Two and a Half



HOTEL PENNSYLVANIA

39TH & CHESTNUT STREETS

PHILADELPHIA, PA.

600 ROOMS
BATHS

RATES { \$2.50 SINGLE WITH BATH
FROM { \$4.00 DOUBLE WITH BATH

Hotel Pennsylvania is the Nearest First-Class Hotel to—

Headquarters of American College of Physicians

University of Pennsylvania

University Hospital

American Oncologic Hospital

Philadelphia General Hospital

Presbyterian Hospital

HOTEL PENNSYLVANIA IS SITUATED AWAY FROM THE NOISE AND BUSTLE
OF DOWNTOWN, BUT WITHIN TEN MINUTES' RIDE OF ANY
POINT OF THE CITY BY TROLLEY, ELEVATED TRAINS
OR THE BUS THAT PASSES THE DOOR

Come once and you will come again

THE DESERT SANATORIUM OF TUCSON, ARIZONA

ALLEN K KRAUSE, M D, *Director*

W PAUL HOLBROOK, M D
Physician-in-Chief

CHARLES W MILLS, M D
Chief, Visiting Staff

MAX PINNER, M D
In Charge Laboratories & Research

¶Offers the facilities and services of its splendidly and completely equipped Out-patient Department for the diagnosis and treatment of acute and chronic disease

¶Caring for both ambulant patients and those confined to bed in quarters outside the Sanatorium

¶Hot, dry, desert climate, especially beneficial for chronic sinusitis, pulmonary affections of various types, hypertension, arthritis, etc

¶Special Department of Physiotherapy Heliotherapy, when indicated, administered under proper safeguards

Accommodations obtainable in Tucson and neighborhood

For information and rates, address Miss B. M. Dickey, Administrative Secretary

The WYATT CLINIC

for

Chronic Arthritis



TUCSON, ARIZONA

Consultation and Advisory Service

ON

HOSPITAL PLANNING

ORGANIZATION

MANAGEMENT

AND EQUIPMENT



SURVEYS CONDUCTED FOR
INDIVIDUAL HOSPITALS OR
ENTIRE COMMUNITIES



Office of

WILLIAM HENRY WALSH, M D
612 North Michigan Avenue
CHICAGO

THE POTTENGER SANATORIUM AND CLINIC FOR DISEASES OF THE CHEST

Monrovia, California



THIRTY YEARS' EXPERIENCE IN THE TREATMENT OF TUBERCULOSIS

LOCATION

Sixteen miles east of Los Angeles In the foothills of the Sierra Madre Mountains, at an elevation of 1000 feet. On the main line of Santa Fe Railway Connected with Los Angeles by interurban railway and splendid boulevards

ENVIRONS

The grounds consist of a beautiful park of forty acres, in which are found a variety of native Live Oaks, subtropical trees and plants, and a profusion of beautiful shrubs and flowers. Many winding walks and nooks of exquisite beauty add to its attractiveness. When on exercise, patients also enjoy the beautiful trails in the adjoining canyons and mountains.

MEDICAL CARE

Competent resident staff. Examinations for comparison every six weeks. Close medical supervision. Their individual needs and problems receive personal attention.

THERAPEUTIC CARE

Fads are not followed, but an endeavor is made to give patients the amount of rest and exercise suited to their individual needs, the benefits of a liberal and adequate diet; such tonic measures as will increase their resistance, and other measures that will help them overcome any disturbing symptoms or complications that may arise. Heliotherapy, tuberculin, pneumothorax and surgery employed whenever indicated.

DIAGNOSTIC CLINIC

A diagnostic clinic is maintained for the study of all diseases of the chest. Weekly rates from \$25.00 up including medical attention, medicines (except expensive specialties) and general nursing. Extra charge for operative measures (except pneumothorax).

F. M. POTTENGER, M.D., Medical Director

For Particulars Address

THE POTTENGER SANATORIUM, Monrovia, California

THE ANALYSIS SHOWS

THE VALUABLE ALKALINE CHARACTER OF

VICHY CÉLESTINS

Natural Mineral Water

INDICATIONS

In stomach and
liver affections
and digestive disorders
in general;
in gout, arthritis
associated with uric
acidemia, uricemia,
and nephrolithiasis of
uric acid origin.



BOTTLED
AT THE SPRING
VICHY, FRANCE

ANALYSIS (GRAMS PER LITER)

Sodium bicarbonate	3 3090
Potassium bicarbonate	0 2490
Lithium bicarbonate	0 0281
Calcium bicarbonate	0.7400
Magnesium bicarbonate	0 1016
Ferrous bicarbonate	0 0012
Sodium chloride	0 3830
Sodium sulphate	0 2430
Silica	0 0300
Sodium arseniate, Phosphate and nitrate	} present

Brochure with Therapeutic Data and Medical Bibliography
sent on request.

Sole United States Agents, American Agency of French Vichy, Inc., 503 Fifth Ave , New York

Eighteenth Annual Clinical Session

**THE AMERICAN
COLLEGE OF PHYSICIANS**

CHICAGO, ILL.—APRIL 16-20, 1934

HEADQUARTERS—THE PALMER HOUSE

In charge of program of general sessions

GEORGE MORRIS PIERSOL, President

1913 Spruce Street, Philadelphia, Pa.

In charge of program of clinics and demonstrations

JAMES B. HERRICK, General Chairman

Peoples Gas Bldg., Chicago, Ill.

COMMITTEE ON CLINICS

ARTHUR R. ELLIOTT, Chairman

30 N. Michigan Ave., Chicago, Ill.

HENRY T. RICKETTS, Graudate School of Medicine, Univ. of Chicago

HUGH A. McGUIGAN, University of Illinois College of Medicine

CHARLES A. ELLIOTT, Northwestern University Medical School

ITALO F. VOLINI, Loyola University School of Medicine

ERNEST E. IRONS, Rush Medical College and Presbyterian Hospital

SOLOMON STROUSE, Michael Reese Hospital

GEORGE W. HALL, St. Luke's Hospital

FREDERICK TICE, Cook County Hospital

ROBERT S. BERGHOFF, Mercy Hospital

JOSEPH BRENNEMANN, Children's Memorial Hospital

Business Management

EDWARD R. LOVELAND, Executive Secretary

133-135 S. 36th St., Philadelphia, Pa.

*An Important Publication***THE DIGESTIVE TRACT****A Radiological Study of its Anatomy
Physiology and Pathology**

By

ALFRED E. BARCLAY, OBE, MA, MD, DMRE
Lecturer in Medical Radiology, University of Cambridge

Formerly Hon Medical Officer in Charge of the X-Ray Department, Manchester Royal Infirmary, and Lecturer in Clinical Radiology, University of Manchester. Sometime President, British Institute of Radiology, Electro-Therapeutic Section, Royal Society of Medicine, Roentgen Society, and Electro-Therapeutic Section, British Medical Association

A fully illustrated quarto volume by one of the leading authorities in this field. The first half of the book is devoted to anatomy and physiology as viewed by the radiologist, and the second half to the diagnosis of pathological conditions.

*Cloth, 4to, 395 pages, 275 illustrations, \$12 00***Other Outstanding Books****HEART DISEASE**

By

PAUL DUDLEY WHITE, MD**\$7 50**

"This book is the most important practical publication on the subject of heart disease that has appeared in this country during the past decade or two. It contains a complete survey of the entire subject, including the diagnosis, prognosis, and treatment of heart disease."

DISEASES OF THE HEART

By

SIR THOMAS LEWIS, MD, DSc, FRCP**\$3 50**

"Lewis, true to form, has accomplished admirably what he set out to do, and for this reason I feel that his book is destined to be used widely as a text and I will certainly recommend it to my classes."—Dr R. Wesley Scott

**CLINICAL DIAGNOSIS:
PHYSICAL AND DIFFERENTIAL**

By

NEUTON S. STERN, AB, MD**\$3 50**

"The more carefully one would study this volume, the more one would be repaid for the time spent upon it."

—N. Y. State Journal of Med.

Part I deals with the technique of history taking and physical examination. Part II covers in a brief and concise form the findings associated with tuberculosis and heart disease. Part III gives a simple and straightforward discussion of the necessary steps in making a diagnosis. Part IV is a discussion of symptoms and signs.

THE MACMILLAN COMPANY

60 Fifth Avenue

New York

BOSTON

CHICAGO

SAN FRANCISCO

DALLAS

ATLANTA

Exclusively Engaged
in providing
Professional Protection
Thirty-Four Years



The Medical Protective Company
of Fort Wayne, Ind.
WHEATON : : : ILLINOIS



THEOCALCIN

(theobromine-calcium salicylate)

A well tolerated diuretic
and myocardial stimulant
indicated in cardiovascular
disease with, or without,
renal insufficiency. . . .

7½ grain Tablets and Powder.

DOSE: 7½ to 22½ grains t. i. d.
with or directly after meals.

Life size and samples upon request

BILHUBER-KNOLL CORP.

134 CROFT AVENUE, JERSEY CITY, N. J.

Devitt's Camp, Inc.

ALLENWOOD
PENNSYLVANIA

(Tuberculosis)

*On beautiful White Deer Mountain, 20 miles southeast
of Williamsport, Pa.*

All modern methods of treatment, including heliotherapy, artificial pneumothorax, phrenic exeresis, Jacobaeus operation, and thoracoplasty

Not operated for profit Moderate rates Modern buildings

Patients given individual attention by experienced physicians and specially trained registered nurses

The following physicians will be glad to examine patients for admittance to Camp

J M ANDERS, M D, Philadelphia, Pa
ISABEL M BALPH, M D, Philadelphia, Pa.
E J G BEARDSLEY, M D, Philadelphia, Pa
WARD BRINTON, M D, Philadelphia, Pa
F W J BURGE, M D, Philadelphia, Pa
DAVID A COOPER, M D, Philadelphia, Pa
DONALD R FERGUSON, M D, Philadelphia, Pa
JOHN B FLICK, M D, Philadelphia, Pa
JOHN A KOLMER, M D, Philadelphia, Pa
W ESTELL LEE, M D, Philadelphia, Pa
A C MORGAN, M D, Philadelphia, Pa
ARTHUR W PHILLIPS, M D, Philadelphia, Pa
GEO MORRIS PIERSOL, M D, Philadelphia, Pa
EDWARD R SNADER, Jr, M D, Philadelphia, Pa
MERVYN R TAYLOR, M D, Philadelphia, Pa
THOS J VISCHER, M D, Philadelphia, Pa
A S KECH, M D, Altoona, Pa
CHARLES C HABLSTON, M D, Baltimore Md
CHARLES S AITKEN, M D, Brookline, Pa.
J C ATWELL, M D, Butler, Pa
F DECARIO, M D, Bradford, Pa
J W WOOD, M D, Chester, Pa

JOHN E FRETZ, M D, Easton, Pa
RICHARD R DALRYMPLE, M D, Erie, Pa
JESSE L LENKER, M D, Harrisburg, Pa
H B ANDERSON, M D, Johnstown, Pa
JOHN H ESBENSHADE, M D, Lancaster, Pa
E J WERLE, M D, Meadville, Pa.
CHARLES G CRANE, M D, Newark, N J
W A WOMER, M D, New Castle, Pa.
EDWARD S MCSWEENEY, M D, New York City
M THERESA SCANLAN, M D, New York City
STANLEY L WANG, M D, New York City
W R GLENNEY, M D, Pottsville, Pa
R R JONES, M D, Pittsburgh, Pa
C L PALMER, M D, Pittsburgh, Pa
A H COLWELL, M D, Pittsburgh, Pa
HOWARD U MILLER, M D, Reading, Pa
A. E DAVIS, M D, Scranton, Pa
H D WILLIAMS, M D, Trenton, N J
B M ALLEN, M D, Wilmington, Del
JOHN MINOR, M D, Washington, D C
J W PEABODY, M D, Washington, D C
H R SCHREIBER, M D, Washington, D C
E W BIXBY, M D, Wilkes Barre, Pa
HARRY M READ, M D, York, Pa

BOOKLET

ROSS K CHILDERHOSE, M D
JOHN S PACKARD, M D
Associate Physicians

WILLIAM DEVITT, M D
*Superintendent and
Physician in Charge*



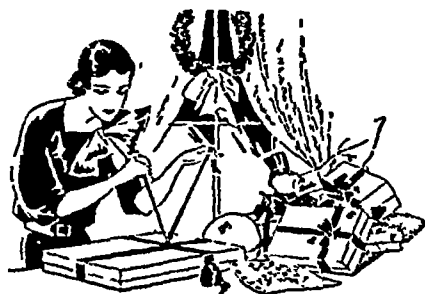
THEY ARE PACKAGED IN BOXES
OF THIRTY-FIVE AND IN
SUFFICIENT NUMBER FOR THE
TREATMENT OF THE DISEASE

THE FINISHED PILLS ARE
PHYSIOLOGICALLY ASSAYED
TO FINALLY CERTIFY THEIR
STANDARDIZATION

THE POWDERED LEAF IS TESTED AND
FOUND TO BE PURELY AND UNADULTERATED
AND IS OF THE HIGHEST QUALITY
AND IS OF THE HIGHEST QUALITY

A FINELY SELF-TESTING
AND IDENTIFIED LEAF POWDER
OF THE HIGHEST QUALITY
AND IS OF THE HIGHEST QUALITY

THE FOUNDATION UPON WHICH THEY
ARE BUILT
AT THE LABORATORIES OF
DAVIES, ROSE & CO., LTD.



"DO UNTO OTHERS"

This will be the happiest
Christmas for many people.
Laughter will have a new
ring, voices a new confidence.
Share some of your joy by
using Christmas Seals on
your letters, packages, gifts,
and cards. The gay little
stamps will brighten your
message. The funds they
provide will help prevent,
find, and cure tuberculosis
throughout the year.



The National Society for the Prevention of
Tuberculosis, Inc., U.S.A.

BUY CHRISTMAS SEALS

Eliminating Doubt from the Electrocardiographic Record



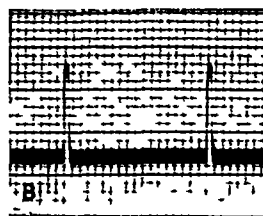
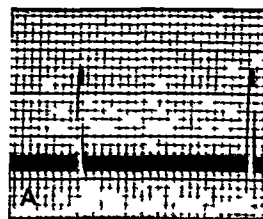
Importance of high and constant speed of deflection

AS explained by a well-known authority, the initial changes in the potentials to be recorded from the heart are rapid, and if the quickest movement of which the galvanometer is capable is too slow to follow these changes, accuracy is lost, distortion occurs when the natural frequency of the galvanometer is below that of the oscillations recorded

In this respect, the Victor Electrocardiograph, due to the principle of tube amplification, precludes any possibility of obtaining an inaccurate record. Regardless of the amount of body resistance, the operator ignores it entirely, for it cannot affect the high speed of deflection that characterizes the Victor instrument. As the galvanometer is permanently set at the factory and sealed in oil, this high speed of deflection is constant under all conditions of operation. There is no string to adjust, no change in operating procedure, no variable to cast doubt as to the accuracy of the record.

Two previous advertisements (copies on request) have explained how the annoying factor of overshooting has been eliminated and

why compensation for skin current is unnecessary with the Victor Electrocardiograph. These are distinct advantages in that they contribute to simplicity of operation, consistent performance and reliable records



DEMONSTRATION

Proving that high resistance has no effect on speed of deflection with the Victor (amplifying type) Electrocardiograph

(A) 10 mm deflection per 1 millivolt input—no external resistance. Note speed of deflection

(B) Same set up of instrument, but with 10 000 ohms non inductive resistance added to external circuit. Note that there is no change in the speed of deflection

Write for complete information on the new model Victor Electrocardiograph, incorporating a timing device and automatic lead markers, and with which either film or paper may be used.

GENERAL ELECTRIC  **X-RAY CORPORATION**

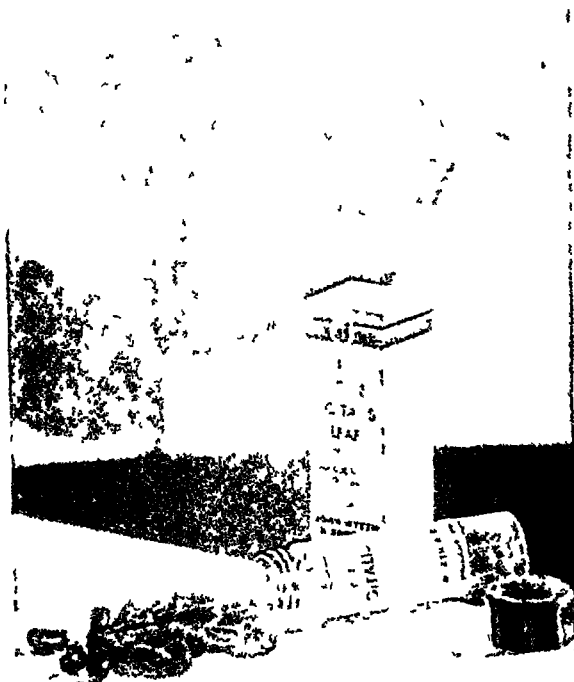
2012 Jackson Blvd.

Formerly Victor X-Ray Corporation

Chicago, Illinois

A DEPENDABLE DIGITALIS

Double Assay
Inspires
Confidence



In addition to assay by the one-hour frog method prescribed by the U. S. P., every batch of Wyeth's Digitalis Leaves is further tested by the cat unit method of Hatcher and Brody. This double check ensures that the strength of each batch is brought to greater uniformity.

In Wyeth's Digitalis you can place the utmost confidence because of its known strength, uniform potency and activity.

WYETH'S CAPSULES DIGITALIS LEAF (DEFATTED)

(Each Capsule contains the equivalent of
one cat unit—15 minims U.S.P. Tincture.)

The advantages of this form of digitalis medication will at once appeal to the clinician and patient—no dropper or measuring device is necessary in order to control dosage. Particularly in the case of the ambulant patient this means less danger of dose variation plus greater convenience of administration.

Supplied in vials of 36 and 100 distinctive green capsules in suitable containers for attaching prescription label for dispensing.

*Control the integrity of your prescriptions
by specifying Wyeth's pharmaceuticals.*



JOHN WYETH & BROTHER, INC.

PHILADELPHIA, PA. and WALKERVILLE, ONT.



ANTIPNEUMOCOCCIC SERUM

Lederle

"Bivalent type I and II antiserum may be used in the treatment of lobar pneumonia in adults before the infecting type is determined, as 40 to 50 per cent of the cases in this locality are caused by types I and II"

*Quarterly Bulletin, Dept of Health,
New York City, 1933, Vol I, p 30*

REFINED and CONCENTRATED ANTIPNEUMOCOCCIC SERUM

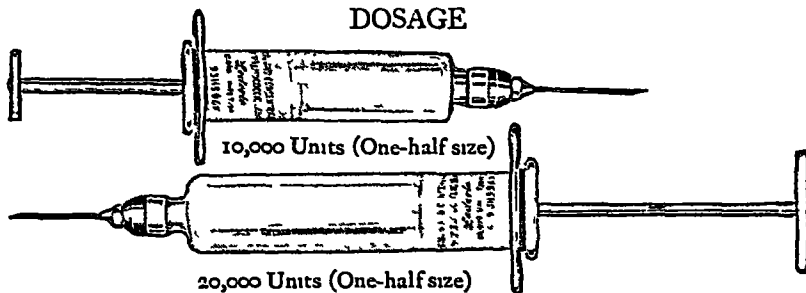
Lederle

AS PREPARED BY FELTON

Packages and Prices

Syringe containing 10,000 units each of Type I and Type II Serum (Bivalent)	\$ 7 00
Syringe containing 20,000 units each of Type I and Type II Serum (Bivalent)	12 00
Syringe containing 10,000 units Type I Serum	7 00
Syringe containing 20,000 units Type I Serum	12 00
Syringe containing 10,000 units Type II Serum	7 00
Syringe containing 20,000 units Type II Serum	12 00
Syringe containing 10,000 units Type VII Serum	7 00
Syringe containing 20,000 units Type VII Serum	12 00

DOSAGE



FIRST DOSE—10,000 units intravenously

SECOND DOSE—20,000 units intravenously Repeat the second dose intravenously at intervals of four to six hours until the temperature falls and beneficial effects are evident

From the standpoint of lower mortality as well as economy of treatment, Antipneumococcic Serum (Lederle) deserves your consideration

LEDERLE LABORATORIES, Inc., New York

A Room and a Bath for Two and a Half



HOTEL PENNSYLVANIA

39TH & CHESTNUT STREETS

PHILADELPHIA, PA.

600 ROOMS
BATHS

RATES { \$2.50 SINGLE WITH BATH
FROM { \$4.00 DOUBLE WITH BATH

Hotel Pennsylvania is the Nearest First-Class Hotel to—

Headquarters of American College of Physicians

University of Pennsylvania

University Hospital

American Oncologic Hospital

Philadelphia General Hospital

Presbyterian Hospital

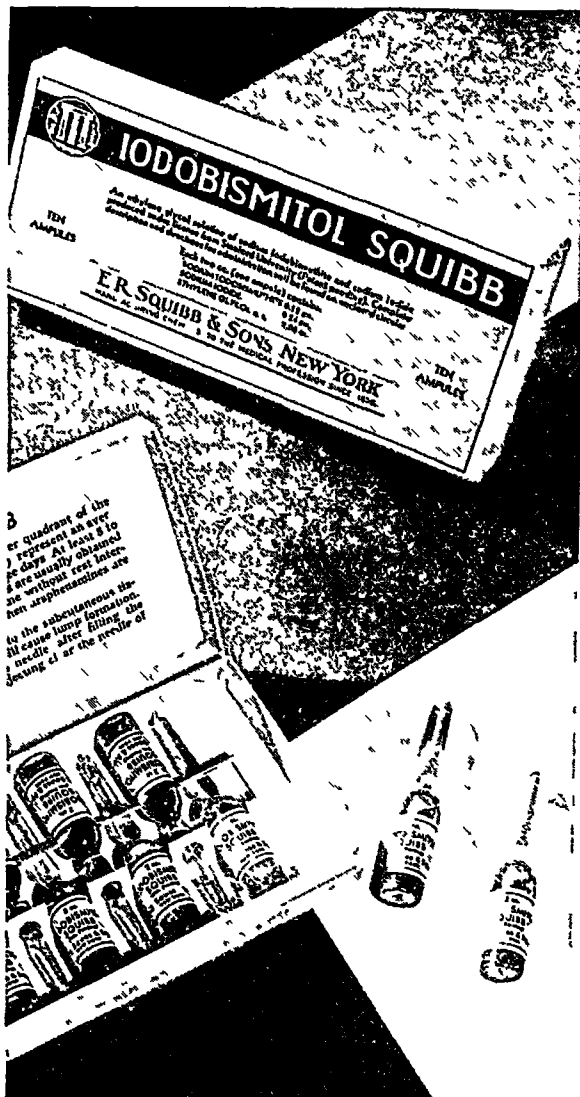
HOTEL PENNSYLVANIA IS SITUATED AWAY FROM THE NOISE AND BUSTLE
OF DOWNTOWN, BUT WITHIN TEN MINUTES' RIDE OF ANY
POINT OF THE CITY BY TROLLEY, ELEVATED TRAINS
OR THE BUS THAT PASSES THE DOOR

Come once and you will come again

IODOBISMITOL SQUIBB

IODOBISMITOL presents bismuth chiefly in an-ion form. Although primarily designed for use as an adjunct to the arsphenamines, Iodobismitol is clinically effective also when used alone—in all stages of syphilis. Repeated doses are well tolerated by the kidneys and by the muscle into which it is injected.

Iodobismitol is a stable solution of sodium iodobismuthite (0.06 Gm per cc) in ethylene glycol containing 12 per cent sodium iodide. It is obtainable only under the Squibb label and is supplied in boxes of 10 and 100, 2-cc ampuls and in 50-cc vials.



E·R·SQUIBB & SONS, NEW YORK
MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

A Safeguard for the Diabetic

INSULIN-STEARN'S

*A Constant, Unvarying
Therapeutic Factor*

The dosage of Insulin must be attuned to the needs of the patient. This means careful calculation on your part, careful observation until the correct formula is reached.

Insulin-Stearns satisfies every requirement.

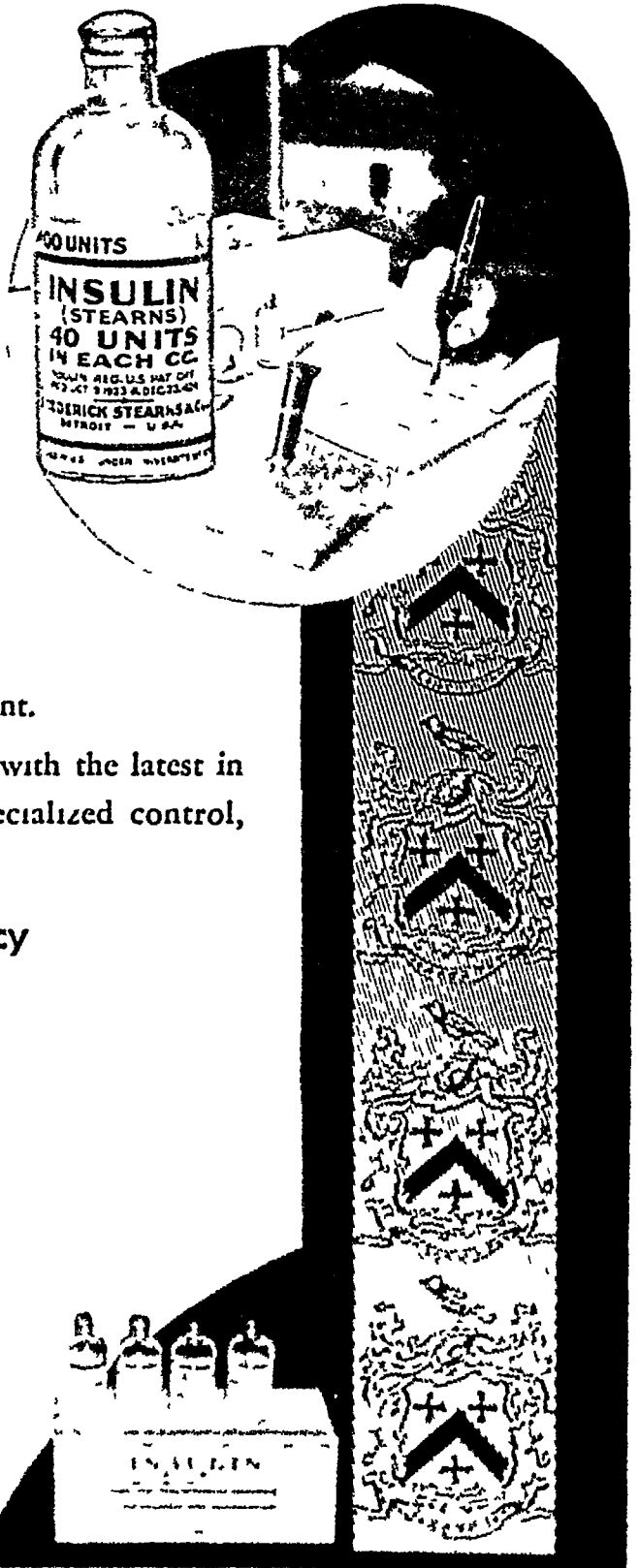
Manufactured in a special plant fitted with the latest in modern equipment, prepared under specialized control, Insulin-Stearns is always:

Biologically exact in potency

Remarkably clear

**Notably free from sting at
point of injection**

Let us send you complete literature describing Insulin-Stearns—how it is made, how it is supplied and recommended for use in actual practice. The facilities of Stearns Insulin Research Department are always at your service.



FREDERICK STEARN'S & COMPANY
DETROIT, MICHIGAN U. S. A.

FREDERICK STEARN'S & COMPANY, INC. DETROIT, MICHIGAN U. S. A. ADM 12
Solely responsible for the production and distribution of Insulin-Stearns in the United States
and Canada.
Solely responsible for the production and distribution of Insulin-Stearns in the United States
and Canada.



Colds are more frequent in children than in adults

AN INTERESTING article in a recent issue of *Hygeia*, entitled, "Cold Facts About Colds," informs us that the incidence of common colds diminishes with advancing age, and, conversely, that it is highest per thousand in the age group from birth through the fourth year—the per thousand incidence in the four-year group being 2430 as compared to 980 in the group 55 years of age or older.

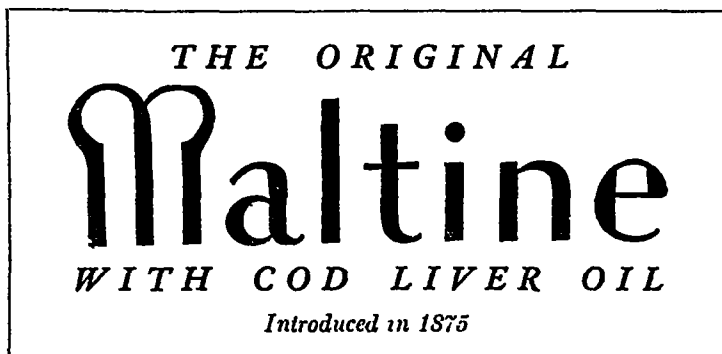
Since the disease itself does not confer immunity and no one has ever identified the ultravirus causing it, it would seem that prevention is the logical means of lowering the high morbidity. Good physical condition, fortified by the ever-helpful vitamins in carefully selected foods, builds up a resistance to bacterial invasion.

It is believed that Vitamin A, origi-

nally known only for its growth-promoting properties, also possesses properties which are anti-infective. The body does not have the power of manufacturing Vitamin A, but it can store the substance in relatively large amounts.**

Maltine With Cod Liver Oil is a potent source of Vitamin A, as well as three other essential vitamins—B (b_1), G (b_2) and D. These vitamin potencies are biologically tested and guaranteed. Maltine With Cod Liver Oil is being prescribed more widely than ever because of its known potency of four different vitamins necessary to normal growth and health. Seventy per cent is Maltine—a concentrated extract of malted barley, wheat and oats. The balance is pure, vitamin-tested cod liver oil. Clinical tests, moreover, indicate that the cod liver oil with Maltine is more readily tolerated than plain cod liver oil. Biological report on request. The Maltine Company, 30 Vesey Street, New York. Established 1875.

** Nutrition and Diet—McLester 1931, ed page 89



MEAD'S VIOSTEROL in HALIBUT LIVER OIL 250 D

economical, efficient
for vitamins A and D

TO HALIBUT liver oil which conforms to standards in New and Non-official Remedies and which has been adjusted* to contain not less than 32,000 vitamin A Units (U S P X) per gram is added sufficient viosterol (activated ergosterol) of previously determined vitamin D value to assure a vitamin D potency of not less than 250 D (or 3,333 Steenbock units per gram).

HIGHLY POTENT IN VITAMIN A

Ten drops of Mead's Viosterol in Halibut Liver Oil 250 D offer approximately 8,000 U S P vitamin A units as compared with 7,700 U S P. vitamin A units supplied by three teaspoonfuls of cod liver oil (standardized at 700 U S. P. vitamin A units per gram)

EQUAL IN VITAMIN D TO MEAD'S VIOSTEROL

Mead's Viosterol in Halibut Liver Oil 250 D supplies the same amount of vitamin D present in Mead's Viosterol in Oil 250 D, the most potent type of antirachitic commercially available. It may therefore be used for the same conditions and in the same dosage as Mead's Viosterol in Oil 250 D from which it differs in that it also supplies generous amounts of vitamin A.

Three teaspoonfuls (the average daily dosage) of standardized cod liver oil containing 60 Steenbock vitamin D units per gram offer 180 units. Ten drops of Mead's Viosterol in Halibut Liver Oil 250 D supply 80 Steenbock vitamin D units (50 of the units are supplied by the Halibut liver oil).

For all the advantages mentioned it may be seen that for both vitamins A and D, ten drops of the product compare favorably with cod liver oil. The effect is not only possible, a quantity of the product is sufficient.

There are other important advantages. (1) In the case of the very young, the product is not only palatable but also easy to administer. (2) The product is standardized and contains no harmful substances. (3) The product is available in a form which is convenient for use.

For further information, please write to Mead Johnson & Company, Evansville, Indiana.

dosage of vitamin D or/and vitamin A is indicated, it is possible to push the dosage of this product without fat intolerance whereas more than four to five teaspoonfuls of cod liver oil daily are usually impracticable.

BIOLOGICALLY ASSAYED

The standard of potency for vitamins A and D in Mead's Viosterol in Halibut Liver Oil is rigidly maintained by constant bioassay. Mead Johnson and Company are fortunate in having a research laboratory with long experience in bioassays. Their background in this field extends to pioneer work with cod liver oil and viosterol.

INDICATIONS

Vitamin A Deficiencies. For such acute deficiencies of vitamin A as xerophthalmia, xerosis, and hemeralopia, Mead's Viosterol in Halibut Liver Oil, when given in proper dosage, is a specific.

Since vitamin A has been held to be of value in maintaining the integrity of the mucous membranes and hence to be a safeguard against the invasion of pathogenic bacteria, Mead's Viosterol in Halibut Liver Oil would seem to be indicated in cases in which it is desired to provide an aid in building up general resistance to body infection. At the present time, vitamin A cannot be regarded as "the anti-infective vitamin."

Vitamin D Deficiencies. Since vitamin D is capable of raising either the serum calcium or the serum phosphorus, depending upon which is in low concentration, Mead's Viosterol in Halibut Liver Oil is indicated where such disturbances of mineral metabolism arise. Where a rapid-acting calcifying agent is required and gastric disturbances must be reduced to a minimum, it is unsurpassed.

Mead's Viosterol in Halibut Liver Oil may be administered for all purposes in which Mead's Viosterol has proved itself valuable, and has the additional advantage of offering generous amounts of vitamin A.

economical for vitamin A:

Mead's Halibut Liver Oil
(without viosterol)

economical for vitamin D:

Mead's Viosterol in Oil
250 D

MEAD JOHNSON & COMPANY, Evansville, Indiana

ANNALS OF INTERNAL MEDICINE

VOLUME 7

DECEMBER, 1933

NUMBER 6

THE PATHOLOGIC ANATOMY OF THE LIVER IN EXOPHTHALMIC GOITER *

By DONALD C BEAVER, M D, and JOHN DEJ PEMBERTON, M D,
Rochester, Minnesota

FOR MANY years icterus has been known as a complication in cases of severe exophthalmic goiter. It has not been demonstrated, however, until fairly recently, that the liver may frequently undergo severe functional and anatomic changes in the syndrome of exophthalmic goiter.

Habershon,¹ in 1874, reported a fatal case of exophthalmic goiter in which jaundice was a complicating feature. Sutcliff,² in 1898, observed jaundice in an extraordinarily acute case of exophthalmic goiter. Eder,³ in 1906, reported three cases of exophthalmic goiter, in each of which jaundice was observed. He commented that Dieulafoy,⁴ in 1901, had described the association of jaundice and exophthalmic goiter in his text, "Pathologie interne." Eder considered that the jaundice arose from some chronic intestinal toxemia, as a possible manifestation of the same intoxication which precipitated the exophthalmic goiter. Chvostek,⁵ in 1917, referred to the occasional development of icterus in severe cases of "morbus basedowi." He considered its appearance a poor prognostic sign, and concluded that it is of toxic origin. Boothby,⁶ in 1922, noted that jaundice was not uncommon in the late stages of long-continued gastrointestinal crises in cases of exophthalmic goiter. He considered it a dangerous sign, and that in most instances it seemed to be an integral part of the syndrome, the direct result of thyroid intoxication. Crotti,⁷ in 1922, stated that it may be observed in a few cases of severe thyrotoxicosis, and that a yellow tint of the sclerotics may rarely be observed in severe, thyrotoxic disturbances of the gastrointestinal tract. He remarked that the prognosis in such cases is always bad, and concluded that the icterus is not due to obstruction of the bile ducts, but is of toxic origin. Assmann,⁸ in 1931, stated that signs of hepatic disturbance, especially icterus, may occur in cases of exophthalmic goiter, and that icterus may be present, without having a causal relationship to the exophthalmic goiter, as a manifestation of catarrhal jaundice, and as the result of cholelithiasis, or of inflammatory conditions of the biliary tract. The

* Submitted for publication August 27, 1932

From the Section on Pathologic Anatomy and the Section on Surgery, The Mayo Clinic.

icterus, however, may be an immediate complication of exophthalmic goiter when there is cardiac decompensation, or it may occur independently of a failing heart as the result of direct toxic influence of the hyperthyroidism. He concluded that icterus, as a complicating symptom of exophthalmic goiter, is found mainly in the most serious cases. The cases, however, do not necessarily terminate fatally.

Evidence to substantiate the intrahepatic origin of the icterus, which also points toward a toxic principle for its etiology, may be found in the literature, based on three types of observation: (1) experimental, (2) clinical evidence of dysfunction of the liver as manifested in the various functional tests for hepatic efficiency, and (3) anatomic changes in the liver.

Farrant,⁹ in 1913, by feeding thyroid to cats, guinea pigs, and dormice, reproduced a modified form of the syndrome of exophthalmic goiter resembling the disease of man. He observed, as a rule, fatty degeneration of the livers of central lobular distribution. Kuriyama,¹⁰ in 1918, found that the glycogen content of the liver of animals fed with thyroid is rapidly decreased to a minimum. Cramer and Krause,¹¹ and others, made similar observations. Hashimoto,¹² in 1921, observed central parenchymal disintegration in livers, varying from simple fatty degeneration to necrosis, in albino rats fed on thyroid in toxic quantities. He also described severe passive congestion, with dismantling of areas about the central veins, sparing only the framework of the liver, and with marked proliferation of Kupffer's stellate cells. He further described regenerative changes in the hepatic cells at the periphery of the affected lobules. In experiments on dogs which were rendered thyrotoxic by feeding desiccated thyroid, Simonds and Brandes,¹³ in 1930, found that even though loss of body weight was severe, the liver did not lose weight. Inanition alone, however, produced loss of weight of both liver and body. In another group of dogs, the proportional loss of weight being slightly greater for the liver than for the body as a whole. They suggested: "Increased functional activity and increased rate of blood flow are probably important factors in the failure of the liver to lose weight in proportion to the body as a whole, in hyperthyroidism." These observations appear to us not to be directly transferable to cases of exophthalmic goiter, since, as will be observed in the cases we are reporting, the liver was usually small.

Younts and Warfield¹⁴ in 1926, established conclusively that hepatic function is impaired in certain cases of thyrotoxicosis. They studied the functional efficiency of the liver by tests of retention, according to the original Retenol technique and modifications of it, by levulose tolerance tests, by the indocyanine blue retention test, by computing the icterus index, and by glutamic oxaloacetic transaminase tests. Cases of adenoma with hyperthyroidism, and of exophthalmic goiter were included in their study. They could observe no correlation between the various chemical factors of the disease and functional efficiency of the liver, except as shown by body weight. Of 12 cases of thyrotoxicosis, 10 had a liver weight which was not affected or affected but to a minor

per cent) They were unable to duplicate the results experimentally in dogs to which thyroid extract had been administered Heilmeyer,¹⁵ in 1931, demonstrated similarly, that by functional tests for hepatic efficiency the function of the hepatic cell was found to be disturbed in half of the cases of exophthalmic goiter which he studied

References to the changes exhibited by the liver in cases of exophthalmic goiter are not abundant Askanazy,¹⁶ in 1898, referred to finding a few cases of cirrhosis and a few cases of atrophic nutmeg liver Marine and Lenhart,¹⁷ in 1911, concluded "In a significant number of long standing cases coming to autopsy, cirrhosis of the liver has been observed In the gross such livers are reduced in volume, sometimes smooth, sometimes slightly granular and again distinctly hobnail The extent of the connective tissue increase varies from a slight thickening of the portal spaces to well marked fibrous bands The liver cells usually exhibit some degree of fatty metamorphosis" Pettavel,¹⁸ in 1912, in describing the anatomic pathologic changes in four cases of morbus basedowii, mentioned that in one case the liver revealed evidence of severe stasis, nodular hyperplasia, massive fatty change, and little content of glycogen, in one case marked cirrhosis, moderate content of glycogen and marked peripheral lobular fatty change, and in one case patchy interstitial hepatitis, and fatty degeneration with depletion of glycogen Matti,¹⁹ in 1912, also found stasis and fatty changes in the livers in cases of morbus basedowii McCarrison,²⁰ in 1917, expressed himself as considering the evidences of toxic action on the liver, such as that reported by Marine and Lenhart, as of great importance, and apparently agreed with their statement based on their observations Kerr and Rusk,²¹ in 1922, described a case of hyperthyroidism in which jaundice developed, and at necropsy the liver presented the appearance of extensive destruction, analogous to that of acute yellow atrophy They considered the hepatic change as a direct expression of the thyrotoxic state Raab and Terplan,²² in 1923, reported a case of morbus basedowii with subacute atrophy of the liver Barker's²³ case, reported in 1930, contained additional evidence of hepatic injury in thyrotoxicosis, in this case the liver was small and necrosis was evident, as also was passive congestion secondary to cardiac failure Weller's²⁴ pathologic review of 44 selected cases of exophthalmic goiter, published in 1930, revealed, in addition to acute degenerative changes, the presence of well marked chronic parenchymatous hepatitis in 22 cases, and of slight hepatitis in 16 cases In only six cases was there no evidence of hepatitis This is the most extensive review of the subject, from the viewpoint of pathologic anatomy, to be found, and leaves little doubt as to the occurrence of severe hepatic injury in certain cases of exophthalmic goiter In a second publication on this topic, Kerr²⁵ stated in 1930 that since the report by himself and Rusk, several other cases had been observed in their clinic, in these cases, the clinical picture was similar, and in the livers of those patients who died, changes were found, similar to those described in the previously reported case Kerr stated further that in the untreated cases

of exophthalmic goiter of long standing, extensive fibrosis has been observed in the liver, and that this may represent the end stages of changes previously described by himself and Rusk. Lewis,²⁸ in 1931, reporting from the Lahey Clinic and the Pathologic Laboratory of the New England Deaconess Hospital, concluded that there was no significant anatomic change in the liver in cases of hyperthyroidism, although in one of the 12 cases included in his report, a small liver (960 gm) was described, which he stated suggested toxic or alcoholic cirrhosis. Assmann, in 1931, considered the most severe stage of toxic injury to the liver in association with exophthalmic goiter to be acute yellow atrophy.

In the investigation to be reported here, a detailed study of the pathologic anatomy of the liver in 107 cases of exophthalmic goiter has been made. The cases were selected, so far as possible, to represent consecutive series over a period of 10 years, excluding from the study only cases of apparent independent hepatic disease, and cases in which other anatomic changes were considered to be possible factors in determining the lesions in the livers. Many of the cases occurred before treatment by iodine was customary, or shortly after such treatment had been introduced. However, the study includes also cases occurring since the time of treatment with iodine.

The clinical history in each case was also carefully reviewed, and correlation of clinical and pathologic features attempted. In order that the pertinent clinical facts of these cases may be appraised, to some extent at least, a summary of the outstanding clinical manifestations will be presented. The cases have been carefully selected to represent only those coming within the designation exophthalmic goiter, as defined by H. S. Plummer.²⁹

CLINICAL DATA

did it consider the type of death unless complicating factors were such as to exclude the case from this study. Such consideration placed the average severity, represented numerically, at 2.75. In only two cases was hyperthyroidism graded 1, in 34 cases it was graded 2, in 56, 3, and in 15 cases, 4. In 26 of the cases (24 per cent), thyroid crisis or verge of crisis was noted, as judged by the severity of the thyroid reaction, cases of post-operative thyroid reaction being excepted. Of the patients with crisis, 20 were females and six, males. The average basal metabolic rate in 95 cases in which it was recorded was +66 per cent. The lowest and highest rates were respectively +16 per cent and +127 per cent. The averages were computed on the basis of highest recorded rate. The average weight of the patients, based on 105 cases in which accurate weights were taken not long before death, was 117 pounds. For the females it was 111 pounds, and for the males, 126 pounds. The lowest recorded weight was 56 pounds and the highest, 180 pounds. The loss of body weight for the group as a whole was 23.9 per cent, of the females it was 22.8 per cent and of the males, 25.14 per cent.

Twenty-three patients (21.5 per cent) had icterus, which was graded by clinical objective estimation from 1 to 4, as follows: in 17 cases the icterus was graded 1, in four cases, 2, in one case, 3, and in one case, 4. In the 17 cases in which icterus was graded 1, the color was frequently observed only in the sclerotics, or it was only ictteroid, but in the six cases in which it was graded 2 to 4 it was well defined to extreme.

PATHOLOGIC DATA WITH CLINICAL CORRELATION

Two outstanding types of hepatic change were observed: acute, and chronic. The acute changes were characterized by fatty metamorphosis, and central or focal necrosis. Frequently more than one of the acute changes were observed in the same liver. The chronic changes consisted of two prominently displayed types of lesions, namely, simple atrophy, and toxic subacute atrophy which in some instances had progressed to actual cirrhosis. The chronic lesions were frequently so blended that all stages and types could be observed in the various preparations of the same liver, in other cases they were distinctly individual. Frequently, both acute and chronic hepatic lesions were found in the same case.

Acute Degenerative Hepatic Lesions. Such lesions appeared in all but nine of the 107 cases, that is, in 91.5 per cent. Their type, grade, and frequency are recorded in table 1. In many cases, more than one type of acute lesion was seen in the same liver, thus accounting for the apparently discordant percentages.

With certain reservations, we agree with Weller's conclusion in respect to the significance of the acute lesions. He stated "It is impossible to attach much importance to such changes because of their very frequent occurrence in a variety of conditions other than thyrotoxicosis." On the other hand, it is impossible completely to ignore them in the face of such a

TABLE I
Acute Degenerative Changes of Liver, 107 Cases of Exophthalmic Goiter

Type of Change	Grade				Total	Per cent
	1	2	3	4		
Fatty changes	53	26	13	2	94	87.8
Central necrosis	31	18	4	1	54	50.4
Focal necrosis	4	2	1	0	7	6.5

A total of 98 cases (91.5 per cent) revealed acute changes.

high percentage of association. From experimental evidence their importance seems confirmed; also, from the fact that they have been the most frequently described hepatic lesions in cases of exophthalmic goiter. Of particular significance in this series is the large number of cases exhibiting actual necrosis, either central or focal (50 and 6.5 per cent, respectively). The occurrence of such changes, especially the more severe changes, may be of considerable importance in the evolution of chronic changes to be described, as well as directly contributing to hepatic dysfunction itself.

It is unnecessary to present a detailed microscopic description of the fatty changes, for the picture was the usual one seen in fatty metamorphosis of the liver. This change was often severe. It usually occupied the central lobular region, although in some instances it was peripheral. When the change was severe, almost all of the cells of the lobule were affected. In some cases one microscopic field would present the picture of simple fatty change and in another field central or focal necrosis could be seen.

Actual necrosis, either of focal or central type, appeared microscopically so frequently that it seemed to represent an accentuation of the same toxic reactions which usually resulted in fatty metamorphosis sometimes pro-

but appeared only in isolated areas. It occurred independently, or in conjunction with the necrotic lesions already described. In only a few instances, however, did it appear to be directly connected with their pathogenesis, although probably the acute lesions were accentuated when passive congestion was severe. Similar acute lesions, however, appeared without congestion.

In consideration of clinical factors relating to exophthalmic goiter, which possibly could influence the development of acute hepatic lesions, the following facts have been adduced. No relationship could be found between age of the patient, sex, or percentage loss of body weight and the occurrence of the acute hepatic lesions. With the exception of loss of body weight, the hepatic lesions appeared to be directly in proportion to the severity of hyperthyroidism, as graded (all factors being considered), or as expressed by individual criteria such as crisis or basal metabolic rate. In the two cases of hyperthyroidism graded 1, 50 per cent of the livers revealed acute degenerative changes, in the 31 cases of hyperthyroidism graded 2, 29 per cent of the livers revealed evidences of acute changes, in 52 cases of hyperthyroidism, graded 3, 48 per cent of the livers had acute lesions, and in the 15 cases of hyperthyroidism graded 4, 100 per cent of the livers exhibited acute changes. The high proportion of acute degenerative changes in cases graded 1 may be on the basis of insufficient numbers. In all cases in which there was crisis, or in which the patients were on the verge of thyroid crisis (26 cases), there were acute hepatic lesions, the hepatic lesions, graded as to severity, occurred as follows in the cases with crisis: 30.8 per cent, grade 1, 38.5 per cent, grade 2, and 30.7 per cent, grade 3. Of 38 cases in which there was a basal metabolic rate of $+60$ per cent or less, in 18 per cent the livers were without acute lesions, whereas in 57 cases in which the basal metabolic rate was more than $+60$ per cent, in only two cases (3.5 per cent) were acute hepatic lesions absent. The more severe acute degenerative hepatic lesions were in the cases in which hyperthyroidism was of relatively short duration, 64 per cent of the acute hepatic changes occurred in cases of duration of one year or less. This is in contrast with the average duration of exophthalmic goiter for the entire number of cases, which was 2.53 years. The fact that most of the cases of exophthalmic goiter of duration of one year or less were the more severe, coincides with the fact that severity of the exophthalmic goiter is the principal factor influencing the development of acute degenerative lesions of the liver.

Chronic Atrophy Atrophy was the most conspicuous, and also possibly the most important hepatic lesion observed. It is impossible to consider atrophy independently of other changes, because of the frequent association of acute changes and other chronic changes in the livers which exhibited atrophy. Nevertheless, the other lesions may be temporarily disregarded, with the understanding that the aspect under consideration is not pathogenesis, but atrophy in a broad, descriptive sense. By the term atrophy we refer to loss of weight of the organ.

More data must be obtained on the normal weight of the liver of human beings, as influenced by age, sex, body weight, stature, or nutritional factors. Until these data have been assembled, a conclusive statement cannot be made concerning the normal weight of the liver. Jackson²⁸ gave the normal average weight of the liver as 1,500 gm, with variability from 1,000 to 2,000 gm, and according to him the weight of the liver is 2.5 per cent of that of the body of a man, and a somewhat higher percentage of that of the body of a woman. Gray's²⁹ figures for the adult were 1,417 to 1,700 gm for men and 1,134 to 1,417 gm for women, constituting about one thirty-sixth of the entire body weight. Vierordt's³⁰ figures were 1,801 gm for men at the age of 25 and 1,648 gm for women at the same age, he gave the percentage of hepatic weight to body weight as 2.75.

Notwithstanding the extreme variability in the weight of the liver, as expressed in the preceding figures, the livers in our series of cases of exophthalmic goiter were usually below the average normal. The average weight of the liver for the entire series of cases was 1,316 gm, for the male it was 1,451 gm, and for the female it was 1,252 gm. The extremes were 644 and 2,450 gm. Curiously enough, the smaller of these two livers revealed only simple atrophy, with slight increase of connective tissue, and the larger advanced cirrhosis with nodular regeneration. The approximate weights of the livers in our 107 cases are given in table 2. It would seem

TABLE II

to be a conservative assumption that a liver of any adult human being, including both sexes, which weighs less than 1,400 gm, represents atrophy. Presuming this to be true, there are 68 cases (63.55 per cent) in this series in which the liver was atrophic.

When the acute degenerative lesions, and lesions of moderate to moderately severe cirrhosis were excluded, there was little microscopic structural alteration from normal in the atrophic livers. In some, however, simple atrophy appeared, in that the hepatic cells were uniformly small, or small only about the central veins, with slight if any increase in connective tissue. In others there was moderate increase in connective tissue about the periportal spaces, with sometimes condensation of periportal structures, so that from four to six or more units appeared in one low power (16 mm) microscopic field (figure 1). In other fields this change was limited to the

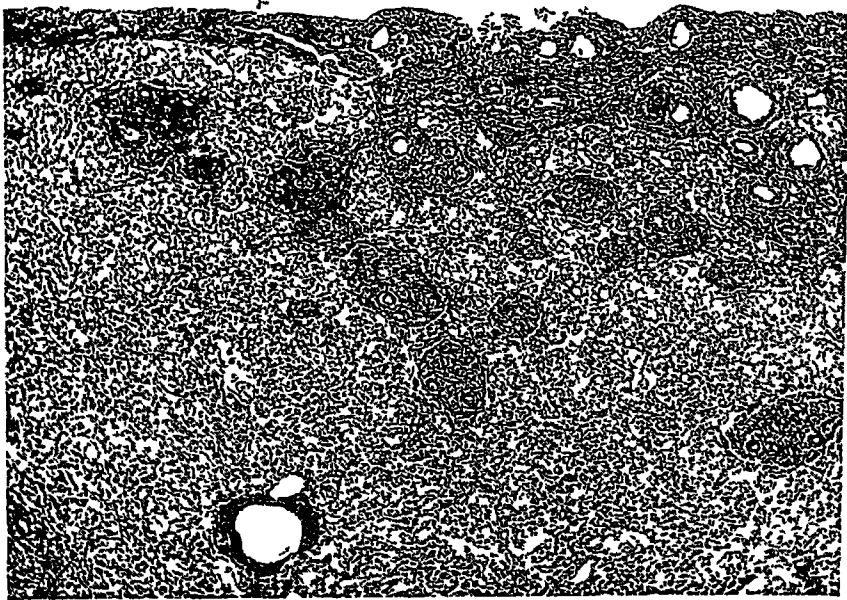


FIG 1 Atrophy with prominent periportal units

hepatic tissue beneath Glisson's capsule. Some zones contained streaks or bands of atrophic hepatic cords appearing to connect central and portal veins, or two adjacent portal veins (figure 2). In the apparently older lesions complete atrophy of certain cords left threads or narrow bands of increase of connective tissue within the lobules (figure 3), around the periportal connective tissue, or extending between two periportal areas. These changes were regarded as those of simple parenchymal atrophy, although it was not always possible to exclude the influence of acute degenerative changes in their pathogenesis.

The factors which, in relation to the syndrome of exophthalmic goiter, could have brought about the loss of weight of the livers, may be adjudged

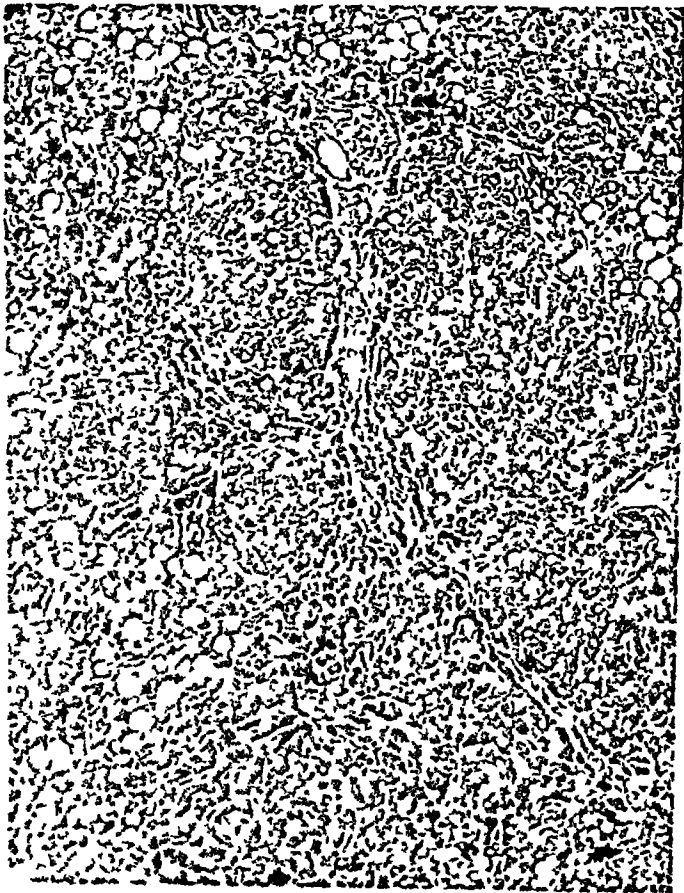


Fig. 2. Sample no. 10, 100x magnification.

by subjecting the anatomic considerations to analysis on the basis of clinical variations. The correlation is rendered difficult because of the frequent association of other pathologic conditions of the liver, which in themselves could have influenced the weight of the organ. Even though the other changes resulted from the syndrome of exophthalmic goiter, the conditions bringing them about may have been somewhat different.

The influence of sex has already been stated, the livers of women were, on the average, 199 gm lighter in weight than those of men. Although the changes according to age were not marked, there was a general tendency for falling off of the hepatic weights from the age of 25 to 30 years, at which the maximal average weight was 1,512 gm, to the age of 70 to 75 years, at which the minimal average weight was 1,096 gm. This decline is graphically revealed in figure 4. There were no significant changes in hepatic

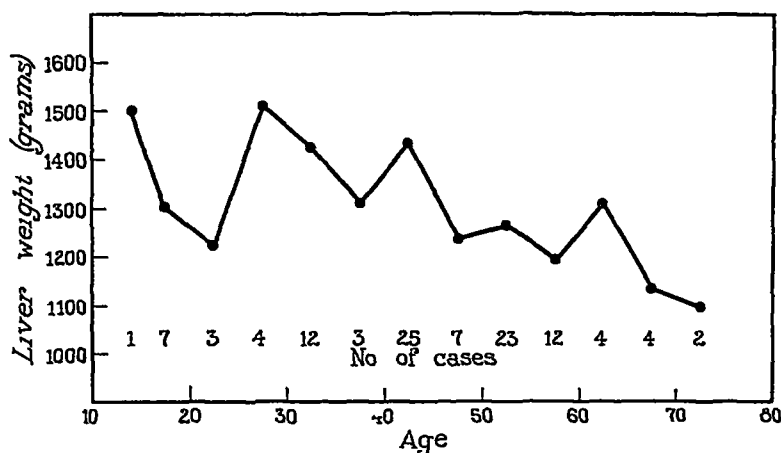
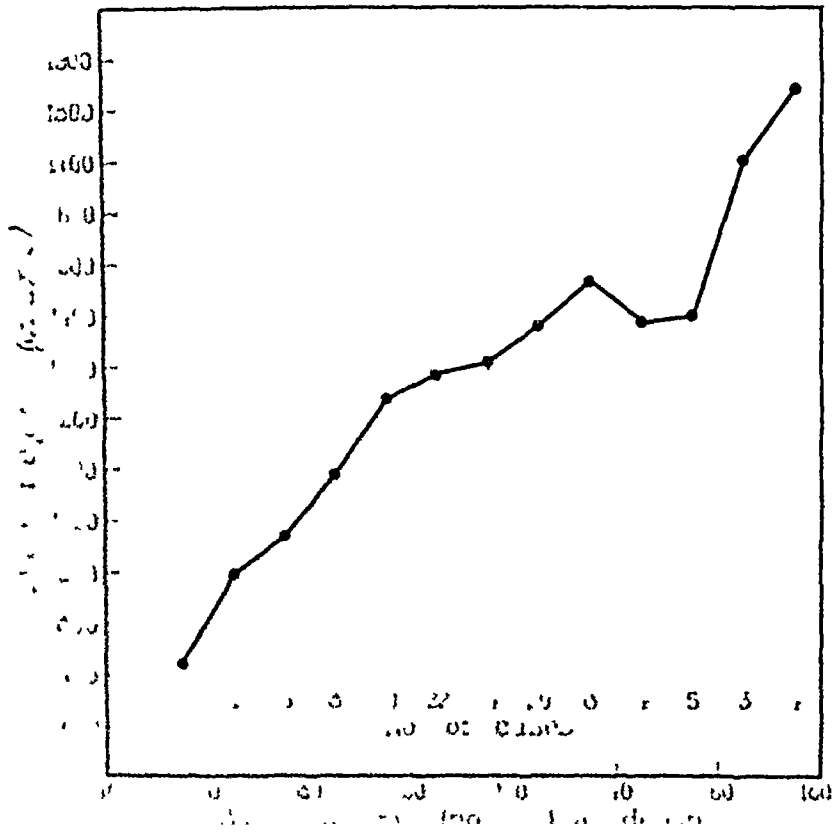


FIG 4 Influence of age on the weight of the liver in exophthalmic goiter

weights when compared with the duration of the hyperthyroid state. Compared with the clinical severity of hyperthyroidism as graded on the basis of all clinical factors, the decline in hepatic weight was proportional to the increase in severity. In the two cases of grade 1 the average hepatic weight was 1,150 gm, in the 34 cases of grade 2 it was 1,418 gm, in the 56 cases of grade 3 it was 1,293 gm, and in the 15 cases of grade 4 it was 1,194 gm. Since there were only two cases of hyperthyroidism of grade 1, one in which there was a relatively large liver, and one in which it was relatively small, little significance can be attached to the exception grade 1 offers to the trend of decrease in hepatic weight in proportion to intensity of hyperthyroidism. In the 26 cases in which there was thyroid crisis or in which the patients were on the verge of crisis, the average hepatic weight was 1,289 gm as compared with 1,316 gm for the entire group. No correlating factors could be determined between hepatic weight and basal metabolic rate. The smaller livers were usually found in bodies of which the weights were relatively small at death, and the larger livers in bodies of greater weight. This relationship is graphically shown in figure 5. These data, however, are not

exceedingly useful, since the same relationship probably exists normally. The percentage of loss of body weight has not been computed against the estimated percentage of loss of hepatic weight, due to inability so far to agree on the normal ratio of weight of liver to weight of body. It is obvious that percentage loss of body weight could not be compared with the weight of the liver at death, without consideration being given for the weight of the liver before loss of body weight occurred. A continuation of this phase of the investigation is contemplated. That the weight of the liver usually remains in a relatively normal ratio to the weight of the body at the time of death does not lessen the argument in favor of the loss of hepatic weight.



changes, and in part on the basis of simple atrophy. The changes of cirrhosis are the terminal stages, or nearly the terminal stages of these lesions. Since the factors of etiology were variable in severity, so also were the lesions which contributed to the cirrhosis, and the lesions of cirrhosis themselves. Thus, varying grades of cirrhosis may be described, grading imperceptibly into the lesions which were pathogenetically related to them. In most instances these changes were progressive, corresponding to subacute or early chronic, toxic atrophy of the liver. In fact, in only one case could the lesion be considered completed and indistinguishable from ordinary atrophic cirrhosis. In table 3 these lesions have been graded, and per-

TABLE III
Chronic Hepatic Lesions of Cirrhotic Type

Grade	Number of Cases	Per cent	Average Weight of Liver, gm
1	48	44.86	1320 (extremes 644 to 2177)
2	13	12.15	1180 (extremes 809 to 1633)
3	2	1.87	1591 (extremes 1100 to 2450)
4	1	0.93	1100
Total	64	59.81	1364

centages for each grade are given. The lesions of grade 1 are those of slight degree, which could hardly be classified as of sufficient development really to constitute cirrhosis. Considering all grades of lesions, this change appeared in 59.81 per cent of the cases, but of more significance is the 14.95 per cent, comprising the cases of cirrhosis of grades 2, 3, and 4, obviously much higher than that found in general material submitted to necropsy. In the material representing grades 2, 3 and 4 the lesions were moderately severe to well advanced.

The microscopic pathologic changes in the cases of cirrhosis in this series were almost identical with the description presented by Weller for his cases. He called the condition interlobular chronic parenchymatous hepatitis, and wrote concerning it as follows: "This is characterized by lymphocytic infiltration, bile duct proliferation and increased stroma in the islands of Glisson. From the usual form of atrophic cirrhosis this picture differs, however, in being much more irregularly distributed in the liver and also in respect to the slight intralobular distribution at the periphery of the lobule, present in the more advanced cases."

The microscopic anatomic changes, presented in detail for the entire 64 cases of cirrhosis, with particular emphasis on the 16 cases in which changes were moderate to severe, revealed a general tendency to increase in connective tissue, either relative or real. The connective tissue was not only extremely variable in amount and in anatomic position of its localization (figure 6), but also extremely variable in its occurrence, from one portion of the liver to another. However, the larger amounts were usually to be found

within or surrounding the periportal spaces, and encroaching to some extent on the periphery of the lobule. In other instances the connective tissue could be identified throughout the lobule, where normal hepatic cords barely persisted in sufficient numbers to identify the lobular unit (figure 7). Or, it was found in the form of perivenous fibrosis about the central veins, or less marked, as small, thread-like bands of connective tissue extending irregularly from the central vein, interposed between the hepatic cords. It sometimes connected the region of the central vein with the portal vein as a connective tissue band and at other times extended between two contiguous portal



FIG. 7. Connective tissue bands of the portal vein.

prominent feature in these cases, although in some the regeneration of parenchyma, as well developed nodular formations (adenomas), was observed

Certain factors had possible influence on the development of chronic cirrhosis, from the standpoint of exophthalmic goiter. Analysis and correlation of the clinical factors will be applied only to the cases in which cirrhosis was graded 2, 3 or 4, because of the mildness of the lesions in those listed as of grade 1. Nine of the 16 patients were women, and seven, men. The average age of the patients with cirrhosis was 52.06 years, of the

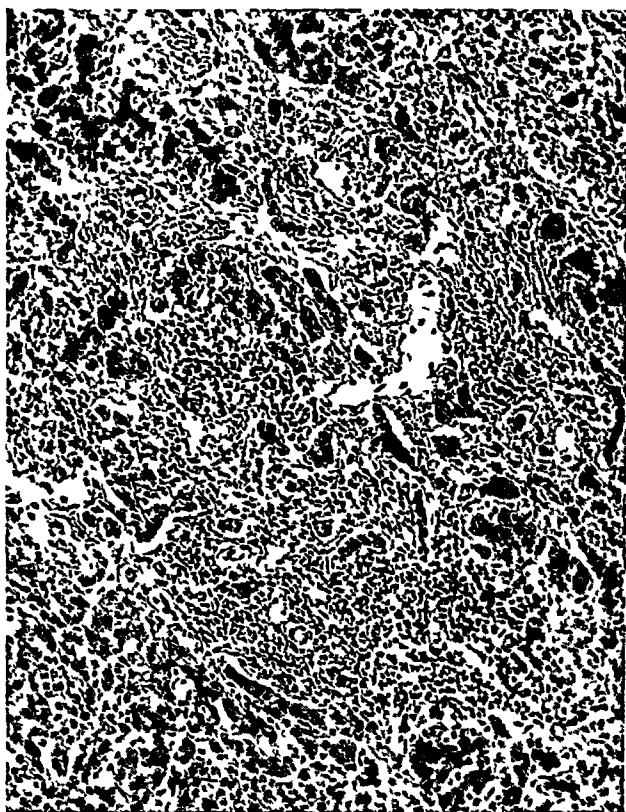


FIG 7 Atrophic cords of hepatic cells with irregular fibrous replacements

women, 53.40 and of the men 48.83 years. The extremes of age were 39 and 66 years. This is in contrast with the average age for the entire group of cases, which was 44.63 years, with extremes of 14 and 72 years. The average duration of hyperthyroidism in cases of cirrhosis was three years and ten months, with extremes of six months and 10 years, whereas for the group as a whole it was 2.53 years, and 64 per cent of the acute hepatic lesions appeared in cases of hyperthyroidism of one year or less in duration. The average severity of hyperthyroidism in this series was 3 (graded on the basis of all factors) in contrast with 2.75 for the entire group. Crisis was a clinical manifestation in only five of these cases. The average basal me-

tabolic rate was ± 80.75 per cent as contrasted with ± 66 per cent for all cases. Percentage loss of body weight in this group was slightly higher than the average of 23.9 per cent for the entire study. In the case of cirrhosis the loss was 29.18 per cent, for the women 30.70 per cent and for the men 27.11 per cent. Icterus was present in seven of the 16 cases.

From anatomic consideration, the livers in the cases of chronic cirrhosis presented an average weight of 1,258 gm (1,160 gm for the women and 1,410 gm for the men) with extremes of 809 and 2,150 gm. This is somewhat less than for the entire series, in which the average hepatic weight

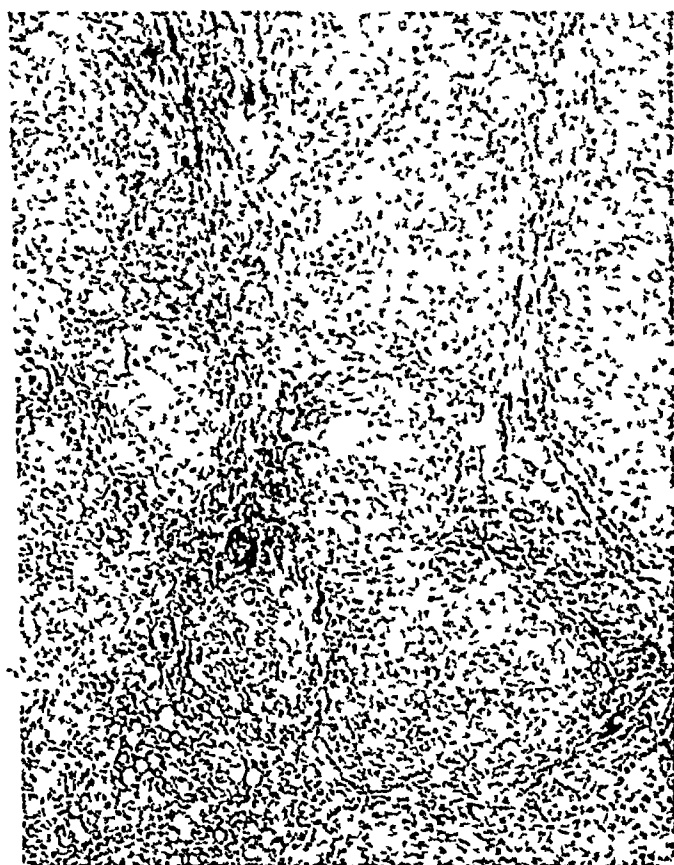


FIG 8 Atrophic cirrhosis with nodules of regenerated hepatic parenchyma surrounded by fibrous connective tissue

was 1,316 gm. Average weight of the spleen in the group with cirrhosis was 245 gm, with variation between 100 and 550 gm. Ascites was present in five cases, but its development was usually terminal, possibly dependent on factors of terminal failing cardiac compensation, too much emphasis cannot be placed on this finding.

Summarizing these data reveals that cirrhosis appears among older patients, with diseases of longer duration and of greater than average severity. These data pertaining to the cases of cirrhosis have been summarized in table 4.

TABLE IV
Moderate and Severe Cirrhosis and Associated Clinical and Anatomic Findings

Case	Age, Years, and Sex	Cirrhosis		Grade of Exoph- thalmic Goiter	Duration of Exophthalmic Goiter	Basal Metabolic Rate, Per cent	Loss of Body Weight,		Weight of Liver, gm	Ascites	Weight of Spleen, gm
		Grade 2	Grade 3 and 4				Per cent	Jaundice			
19	46F	+	—	3	5 yrs	+102	0	0	1025	0	162
20	50F	+	—	4	2 yrs	+91	+	+	1525	0	325
24	59M	+	—	3	6 mo	+73	0	+	1600	0	125
30	39M	—	+	4	2 yrs	—	0	+	1225	3000 c c	550
31	52M	+	—	3	6 yrs	+44	0	+	1300	1500 c c	230
32	59F	+	—	3	14 mo	+104	0	0	975	3000 c c	100
38	66F	+	—	3	6 yrs	+98	0	0	900	0	120
42	63M	+	—	3	15 mo	+61	0	37	809	3000 c c	180
56	43F	+	—	4	5 yrs	—	+	+	1005	0	257
58	40M	—	+	4	5 yrs	+102	+	+	2450	0	515
64	63F	+	—	4	10 yrs	+114	+	+	1100	0	110
65	57F	+	—	3	1 yr	—	+	0	1425	0	200
85	52F	—	+	1	5 yrs	+38	0	0	1100	0	205
99	42M	+	—	3	11 mo	+73	0	0	1633	0	395
105	56M	+	—	3	3 5 yrs	+69	0	37	957	0	292
106	46F	+	—	2	3 yrs	—	0	27	1100	1000 c c	160
Total or average	52	13 (12 per cent)	3 (2 8 per cent)	3+	3 yrs 10 mo	+ 80 75	5	29	1258	5 cases	245

Icterus in Association with the Acute and Chronic Lesions With the clinical discussion, mention has been made of the occurrence of icterus, but because of its pathologic importance brief consideration will be given, to facilitate its interpretation. It should be remembered that cases which were thought to represent previous or independent hepatic or biliary obstructive disease were excluded from this study, so that icterus on that basis need not be considered here. The data concerning icterus are summarized in table 5.

Icterus occurred in 23 cases (21.5 per cent) of this series, 10 of the patients were males and 13, females. It was of moderate to extreme grade in six cases and mild in 17. The average age of the patients who exhibited this change was 48.17 years, as compared with 44.63 years for all cases. For the males the average age was 56 years, and for the females, 42.15 years. Icterus was observed in the more severe cases. As judged by all clinical criteria, it appeared in cases with an average severity of grade 3, as compared with severity of grade 2.75 for the entire study. The average duration of hyperthyroidism in the cases in which there was icterus was not materially different than for the entire study, namely, 2.38 years as compared with 2.53 years. Seven patients with icterus were in, or on the verge of, thyroid crisis before death. The basal metabolic rate was exactly the same for the cases with icterus as for the entire number of cases. The percentage loss of body weight was 29.52 per cent in the series with icterus, as compared with 23.9 per cent for the cases as a whole.

The average hepatic weight, in cases in which jaundice was a clinical manifestation, was essentially the same as for the entire study, 1,348 gm. compared with 1,316 gm. Cirrhosis was present to some degree, although usually slight, in 19 of the 23 cases. It was graded 1 in 12 cases, and 2 or 3 in seven cases (30.4 per cent). Acute degenerative lesions were present in all cases. The changes were (1) fatty metamorphosis in 21 cases, graded 1 in nine cases, 2 in six cases, and 3 in six cases, and (2) focal or central necrosis, or both, in 18 cases, graded 1 in eight cases, and 2 or 3 in ten cases. In cases 6, 35, 77 and 81 (table 5) the hepatic changes, as judged anatomically, appeared not to be of sufficient severity to account for icterus, although mild changes existed in these cases.

In consideration of all cases from the viewpoint of probable hepatic dysfunction, whether icterus was present or not, it was estimated that lesions of sufficient severity to reveal hepatic dysfunction by dye tests or other tests of hepatic function existed in approximately 40 per cent of the cases, this estimate compared favorably with the figure of 50 per cent recorded by Youmans and Warfield who actually applied these tests. This phase of the subject, tests for hepatic function, is being investigated at present and will be reported subsequently.

Of interest, and of possible significance, was the mild to rather intense accumulation of bile pigment in the hepatic cells of the central lobular zones, in cases with or without jaundice, indicating the inability of the hepatic cells

TABLE V
Correlation of Icterus and Clinical and Anatomic Findings

Case	Age in Years, Jaundice, and Sex	Grade	Duration of Exophthalmic Goiter	Clinical Grade of Exophthalmic Goiter	Basal Metabolic Rate, Per cent	Loss of Body Weight, Per cent	Crisis	Weight of Liver, gm	Cirrhosis of Liver, Grade	Fatty Change, Grade	Central Necrosis, Grade	Focal Necrosis, Grade
1	52M	1	10 yrs	3	+ 67	30	0	1100	1+	2	0	0
6	14F	1	9 mo	2	+ 31	7	0	1500	0	1	0	0
20	50F	2	2 yrs	4	+ 91	36	+	1525	2	2	0	0
24	59M	3	6 mo	3+	+ 73	14	0	1600	2	3	2	0
28	15F	1	9 mo	4	+ 61	48	0	1725	0	1	2	0
30	39M	2	2 yrs	4	—	29	0	1225	3	1	3	2
31	52M	2	6 yrs	3	+ 44	49	0	1300	2+	1	1	0
35	38F	1	8 mo	3	+ 102	39	0	1500	1	0	1	0
76	40F	1	5 yrs	3	+ 93	23	+	1200	1	2	1	0
77	58M	1	4 mo	2	+ 61	36	0	1675	1	1	0	0
78	66M	1+	8 mo	3	+ 64	28	0	1300	1	2+	1	0
81	40F	1	3 mo	2	+ 31	8	0	1193	0	0	1	0
82	74M	1	2 yrs	2	+ 42	29	0	1395	1	2+	2	2
83	54F	1	1 yr	3	+ 32	29	+	1088	1	3	3	3
93	43F	1+	10 mo	3	+ 83	25	0	1840	1	3	2	0
95	57M	1	1 yr	4	+ 80	40	+	1090	0	1	2	1+
41	42F	1+	6 mo	3	+ 54	44	+	1520	1+	3+	1+	0
42	63M	1	15 mo	3	+ 61	37	0	809	2	1	2	0
44	58F	1	3 mo	3	+ 80	37	0	794	1	2	2	0
56	43F	4	5 yrs	4	—	26	+	1005	2	1	1	0
58	40M	1	5 yrs	4	+ 102	6	+	2450	3	3	0	0
66	52F	2+	8 yrs	3	—	*	0	1270	1	3	3+	0
107	59F	1	14 mo	3	—	?	0	952	1+	3	1	0
Total or average	48+	17	2 3 yrs	3+	+ 66	29 52	7	1348	19	21	18	4

* Emaciation, graded 4

to excrete satisfactorily, with consequent accumulation of biliary pigments in the functionally impaired hepatic cells. In no instance was anatomical obstruction to flow of bile a part of the picture.

Five of the cases of icterus were associated with passive congestion of the liver of relatively severe grade. In case 35, not having any other adequate explanation, this finding could be used to explain the icterus, for it is known that passive congestion of the liver and icterus may be associated conditions. In the remaining cases, passive congestion is not needed to explain the icterus, unless one indirectly considers that the passive congestion favored the formation of other anatomic changes in the liver, which in themselves were sufficient to account for its occurrence.

In summarizing, we may state that the anatomic explanation for the occurrence of icterus usually rests on the basis of clearly demonstrable alterations of hepatic tissue. In four cases only was this anatomic explanation considered inadequate. Icterus seems to occur in two types of cases, in both of which atrophy is the outstanding condition: (1) cases of shorter but more severe hyperthyroidism in which atrophy and acute toxic changes predominate, and (2) cases of longer, relatively less severe hyperthyroidism, in which terminal acute changes are superimposed on a liver exhibiting atrophy and some degree of cirrhosis.

SUMMARY AND CONCLUSIONS

Analysis was made of the pathologic anatomy of the liver and the correlated clinical findings in 107 cases of exophthalmic goiter.

Three types of hepatic lesions predominate in exophthalmic goiter: (1) acute degenerative lesions (fatty metamorphosis, focal and central necrosis, and changes secondary to stasis of blood), (2) simple atrophy, and (3) subacute toxic atrophy and toxic cirrhosis.

The frequency of these lesions was as follows: (1) acute lesions 91.5 per cent, of which fatty metamorphosis composed 87.8 per cent, central necrosis 50.4 per cent, and focal necrosis 5.6 per cent, (2) atrophy 63.55 per cent, in which cases the average weight of the liver was 1,316 gm., and (3) subacute toxic atrophy and cirrhosis 59.81 per cent, of which lesions of grade 1 composed 44.86 per cent, lesions of grade 2, 12.15 per cent, lesions of grade 3, 1.87 per cent, and lesions of grade 4, 0.93 per cent.

Jaundice was present in 23 cases (21.5 per cent). The hepatic lesions are usually adequate to account for the presence of icterus, and in addition, including cases without jaundice, they are sufficient probably to cause disturbances of hepatic function detectable by clinical tests of hepatic efficiency in approximately 40 per cent of the cases.

The common factor in the evolution of these lesions appears to be severity of the syndrome of exophthalmic goiter.

The acute lesions are not usually influenced in their occurrence or severity by the age of the patient, the sex, or the percentage loss of body weight. Except for the loss of body weight, the acute lesions usually occur

directly in proportion to severity of the disease. They appear most prominently in the more severe cases of shorter than average duration.

Atrophy is more pronounced among females than males, and appears to be more marked among the aged than the young. It is proportional to severity of the disease, with the exception that it seems not to be correlated with basal metabolic rate. The duration of the disease does not appear to be a factor. The smaller livers were observed in the smaller subjects, and the larger livers in the larger subjects. The relationship of the weight of the liver to loss of body weight, however, will constitute an independent study.

The changes of subacute toxic atrophy and cirrhosis appear more frequently among females than males but the difference in incidence, according to sex, is not greater than in the entire study. These lesions appear among older patients, among whom the disease is of longer duration and of more than average severity.

We may conclude, as Boothby did in speaking of jaundice in exophthalmic goiter, that in most instances the lesions in the liver appear to be an integral part of the syndrome of exophthalmic goiter, and that they are due directly to thyroid intoxication, since, as we have found, they are usually intimately related in their severity, to the intensity and the duration of the disease. It is probable that the hepatic changes are not only related to the hyperthyroid state, but also to the toxic factor of exophthalmic goiter, which Plummer believes exists, for in experimentally produced hyperthyroidism, induced in animals by feeding thyroid substance, lesions comparable to those we have described have not been produced. Atrophy, acute degeneration, and cirrhosis are probably interrelated conditions, each with a sequential pathogenetic relationship to the other, and each intimately concerned with the hyperthyroid state and the toxic factors as elaborated in the syndrome of exophthalmic goiter.

BIBLIOGRAPHY

- 1 HABERSHON, S. O. Exophthalmic goiter, heart disease, jaundice, death, *Lancet*, 1874, 1, 510.
- 2 SUTCLIFF, E. H. An extraordinarily acute case of Graves' disease, *Lancet*, 1898, 1, 717.
- 3 EDER, M. D. Three cases of jaundice occurring in persons suffering from exophthalmic goiter, *Lancet*, 1906, 1, 1758.
- 4 DIEULAFOY, G. Quoted by Eder.
- 5 CHVOSTEK, F. *Morbus Basedowi und die Hyperthyreosen*, 1917, Julius Springer, Berlin.
- 6 BOOTHBY, W. M. Part 4. *Diagnosis and treatment of the diseases of the thyroid gland*, 1922, Oxford Medicine, Oxford University Press, New York, 111.
- 7 CROTTI, A. *Thyroid and thymus*, 1922, Lea and Febiger, Philadelphia.
- 8 ASSMANN, H. *Leber und Milz bei Morbus Basedow*, *Munchen med Wchnschr*, 1931, 1xxviii, 221-225.
- 9 FARRANT, R. Hyperthyroidism: its experimental production in animals, *Brit Med Jr*, 1913, 11, 1363-1367.
- 10 KURIYAMA, S. The influence of thyroid feeding upon carbohydrate metabolism. I. The storage and mobilization of the liver glycogen in thyroid-fed animals, *Jr Biol Chem*, 1918, xxxiii, 193-205.

- 11 CRAMER, W., and KRAUS, R. A. Unilateral atrophy of the thyroid gland: the effect of thyroidectomy on the distribution of the nitrogen distribution in the urine, *Proc. Soc. Exptl. Biol. Med.*, 1922, **xxv**, 550-560.
- 12 HASHIMOTO, H. Heart in experimental hyperthyroidism: a histological study, *Endocrinology*, 1921, **v**, 549-560.
- 13 SIMON, J. P., and BAILEY, W. W. Effect of experimental hyperthyroidism on heart, liver and kidney, *Arch. Path.*, 1909, **xv**, 115-119.
- 14 YOUNG, J. B., and WARD, I. M. Liver injury in hyperthyroidism: decreased functional efficiency, *Arch. Int. Med.*, 1925, **xxv**, 1-14.
- 15 HEIMANN, L. Blutstoffwechselstudien I. Mitteilung: Beeinträchtigung der Funktion beim Morbus Basedow, *Deutsch. Arch. f. Klin. Med.*, 1911, **cxvii**, 812-825.
- 16 ASKANAZY, M. Pathologisch-anatomische Beiträge zur Kenntnis des Morbus Basedow, insbesondere über die dabei auftretende Muskelerkrankung, *Deutsch. Arch. f. Klin. Med.*, 1898, **lxv**, 118-186.
- 17 MARINI, D., and LESHARE, C. H. Pathological anatomy of exophthalmic goiter: the anatomical and physiological relation of the thyroid gland to the disease, *Arch. Int. Med.*, 1911, **viii**, 265-316.
- 18 PERTWILL, C. A. Beitrag zur pathologischen Anatomie des Morbus Basedow, *Deutsch. Zschr. f. Chir.*, 1912, **cxvi**, 488-513.
- 19 MARINI, D. Quoted by Chvostek.
- 20 MCCARRISON, R. The thyroid gland in health and disease, 1918, Wm. Wood and Company, New York.
- 21 KERR, W. J., and RUSK, G. Y. Acute yellow atrophy associated with hyperthyroidism, *Med. Clin. N. Am.*, 1922, **vi**, 445-459.
- 22 RYAN, W., and TERPLAN, C. Morbus Basedow mit subakuter Leberatrophie, *Med. Klin.*, 1923, **xix**, 1154-1156.
- 23 BARKER, L. F. Thyro-toxication with necrosis and atrophy of liver, damage to heart muscle and kidneys, and terminal bronchopneumonia, *Med. Clin. N. Am.*, 1930, **xiv**, 261-263.
- 24 WETTER, C. V. Hepatic lesions associated with exophthalmic goiter, *Trans. Assoc. Am. Phys.*, 1930, **xlv**, 71-76.
- 25 KERR, W. J. Necrosis of heart and liver in thyrotoxicosis with some notes on possible changes in other organs, *Northwest Med.*, 1930, **xxix**, 430-431.
- 26 LEWIS, W. Hyperthyroidism and associated pathology, *Am. Jr. Med. Sci.*, 1931, **clxxxi**, 65-74.
- 27 PLUMMER, H. S. Part 2. The function of the thyroid gland, *In* Mayo, C. H., and PLUMMER, H. S. The thyroid gland, The Beaumont Foundation Lectures, Series 4, 1926, C. V. Mosby Company, St. Louis.
- 28 JACKSON, C. M. *In* MORRIS' human anatomy, 1914, P. Blakiston's Son and Company, Philadelphia.
- 29 GRAY, H. Anatomy, descriptive and surgical, 1908, Lea and Febiger, Philadelphia.
- 30 VIERORDT, K. H. Anatomische, physiologische, und physikalische Daten und Tabellen, 1906, G. Fischer, Jena.

BROMIDE PSYCHOSES: DIAGNOSIS, TREATMENT AND PREVENTION *

By MAX LEVIN, M D , *Harrisburg, Pennsylvania*

THAT psychoses may occur as a symptom of bromide intoxication has been known for many years, but only since 1925, when Hauptmann described a modification of Walter's¹ method for determining the concentration of bromides in the serum, has it been possible to diagnose them with ease. Before 1925 bromide psychoses doubtless were overlooked as frequently as syphilis in the days before the Wassermann test.

In spite of the help given by the Walter-Hauptmann test, the recognition of a bromide psychosis is not always a simple matter. The difficulty is very much like that sometimes encountered in cases of syphilis. A positive Wassermann reaction tells us that the patient has syphilis, but not whether the lump palpable in his abdomen is a gumma or some other kind of tumor. Similarly, when the Walter-Hauptmann test discloses a high¹ concentration of bromides in the serum, we know that the patient has a bromide intoxication, but from that alone we cannot tell whether his psychosis is due to bromides. The answer to this question depends on the following criteria:

1 We must know whether the psychosis began before or after the intoxication began. It is important not to confuse the bromide psychosis and the underlying neurosis or psychosis for which bromides were administered. Let us consider the example of a patient who begins to show the symptoms of a depression in January, in March he begins to take large daily doses of bromides, and in May he enters a delirium. If we now see him for the first time, and learn that he began to be psychotic two months before he began to get bromides, we might hastily exclude bromide psychosis from consideration. This would be a mistake, for in addition to the basic depression the patient now has a delirium that began *after* he became intoxicated.

2 We must consider the duration of the psychosis after the discontinuance of the bromides. Usually a bromide psychosis clears up within a

* Received for publication August 12, 1933

From the Harrisburg State Hospital

¹ The consensus of opinion is that a concentration of 150 or more milligrams of bromide per 100 cubic centimeters of serum warrants one in speaking of a bromide intoxication. Physicians must bear in mind two considerations. 1 It is possible that future research will show that some persons, abnormally susceptible, may develop bromide psychoses even before the concentration in the serum has reached 150 mg. 2 In evaluating the results of the bromide test one must consider the date of the test in relation to the date of discontinuance of the bromides. Suppose a man receives bromides until June 1, and I see him for the first time on June 28, at which time the bromide concentration is 75 mg. I would be greatly in error were I to conclude that the bromide concentration being only 75, the patient's recent symptoms could not be the result of a bromide intoxication. A concentration of 75 *four weeks after discontinuance* would indicate that at the time of discontinuance the patient was loaded with bromides. Charts showing the rate at which the bromide concentration falls after discontinuance may be found in O. Wuth's² article.

short time—generally from two to six weeks—after discontinuance.* Here again we must be careful not to confuse the bromide psychosis and the underlying psychosis. In the hypothetical case cited above we will suppose that several weeks after discontinuance the delirium clears up, after which the patient continues for many months to show symptoms of depression. In this event it would be a mistake to argue that, discontinuance having led to no recovery, bromide psychosis may be excluded; correct diagnosis will be possible only if we recognize that the patient had *two* psychoses: (a) a depression, which began before the intoxication and now continues after the intoxication has subsided; and (b) a delirium, which began during, and cleared up simultaneously with, the intoxication.

If we bear in mind these considerations we shall rarely be misled by the Walter-Hauptmann test into diagnosing a bromide psychosis where none exists. To demonstrate their importance I have selected the following case, in which a bromide delirium occurred in a woman who had general paresis. The case is of special interest because of the well-known fact that bromide intoxication sometimes simulates general paresis.

CASE REPORT

A woman of 42 was admitted to the Harrisburg State Hospital on June 29, 1932, in a delirium.

Present Illness The sisters of the patient stated that one year before admission she began to complain of fatigue. It tired her, for example, to spend an hour or two downtown. In December 1931, her speech began to be affected, she stammered and halted, and her enunciation was not clear. At the end of May 1932 "her mind began to wander." *One week before admission disorientation was noticed for the first time.* While in her own bedroom she said, "I want to go home and be in my own bedroom." She saw imaginary babies in the room. During the week before admission she was so incoordinate as to be unable to walk.

Medication The relatives stated that during the year before admission she was under the care of a physician, who gave her "nerve medicine" for an unbroken period of approximately six months, ending at the time of her admission.

Mental Examination The patient was cooperative but very dull. There was marked difficulty in thinking of words. She was disoriented in all spheres. Her memory was poor.

Physical Examination The patient was feeble and looked very old for her years. She was undernourished, her height being 5' ½" and her weight only 92 pounds. The pupils were of moderate size and irregular, the left was larger than the right, there was no reaction to light and only the barest reaction on accommodation. Speech was badly slurred. There was a coarse tremor of the tongue and fingers. Gait was slow and unsteady, and she was unable to stand with her feet together. The knee-jerks and ankle-jerks were hyperactive and equal. The physical examination otherwise showed nothing of importance.

Laboratory Examinations The Walter-Hauptmann test on June 30, 1932, showed 350 milligrams of bromide per 100 c c of serum, July 13, 200 milligrams. The Wassermann reaction of the blood was negative. Spinal fluid Wassermann reaction, plus 4, globulin, positive, cells, 3, mastic curve, 5555543000.

* There is no uniformity as to the level to which the serum bromide concentration must fall before a bromide psychosis clears up. In some cases a bromide psychosis clears up long before the concentration falls to 150 mg., in others the concentration must first fall to 150 or less.

Course in Hospital The patient emerged from her delirium on July 8—her tenth day in the Hospital. On that day she said, "I am beginning to be able to get my mind together and remember things. I don't jumble my words any more like I used to. Do you remember? Poor Mother never used to understand me, people had to tell her what I was trying to say. Now I speak plain." (Tell me more about the state of your mind at that time.) "I forgot everything. I'd start to say something and then I'd ask, 'What was I saying?'" Mother was crying all the time—she was afraid I'd never get my speech back." (When you came here, did you know where you were?) "No. I asked the girls (nurses), 'Where am I? What is this place?'" When they told me I was so near home, I couldn't believe it, I thought I was near Philadelphia." Throughout the remainder of her stay in the Hospital the patient was at all times clear and well oriented.

Neurological reexamination on July 8 showed that the pupils now reacted moderately well on accommodation. They still showed no reaction to light. Speech was still slurred, but less so than on admission.

Following her recovery from the delirium the patient gained weight rapidly. Whereas on admission she had looked aged and worn out, she now began to look normally youthful, her facial expression being alert and animated. On September 2, 1932, she was inoculated with malaria. The first paroxysm occurred on September 10. Paroxysms occurred infrequently, the fifth and last occurring on September 27. Thereafter fever therapy was continued with the aid of injections of typhoid vaccine and hot packs. She continued to gain weight. She was paroled on December 10, 1932, weighing 116 pounds.

Catamnestic Note On March 11, 1933, reexamination gave the following results. She looked and felt well and was in excellent spirits. "I couldn't feel better." Memory, subjectively, was good. She retained seven digits. Calculation was not good. Thus, in subtracting successive 7's from 100, her performance during one minute was as follows: 93, 76, 89, 82, 75, 68, 61, 54, 48. The pupils were of moderate size, approximately equal, and irregular, they reacted moderately well on accommodation but were fixed to light. There was a moderate tremor of the face, tongue, and fingers. There was very slight slurring of speech, she had especial difficulty with "artillery." When asked to write "Methodist Episcopal," she wrote, in one word, "Methodistesepiscopal," crossing the first "t" but not the second. The knee-jerks were hyperactive and equal. The ankle-jerks were active and equal. She swayed slightly when standing with feet together and eyes closed. Reexamination on June 10, 1933, gave substantially the same results.

COMMENT

This case shows the importance of bearing in mind the mental disturbances arising from bromide intoxication. A physician unfamiliar with bromide intoxication might, on the patient's admission to the Hospital, have attributed all of her symptoms to general paresis. In view of the fact that she was then delirious, he might have concluded that her paresis was relatively advanced. In truth, she had paresis in a relatively early state. The symptoms that had caused her to be admitted to the Hospital were not those of paresis but of bromide delirium, the diagnosis of which is established by (1) the disclosure of a severe bromide intoxication by the Walter-Hauptmann test, (2) the fact that the delirium had begun not more than one month before admission, and about five months after she had begun to take "nerve medicine", (3) the clearing up of the delirium a short time (10 days) after the discontinuance of the bromides.

Attention is called to the absence of a rash in this case. Absence of a rash does not exclude bromide intoxication.

Attention is called also to the fact that at the height of the intoxication the pupils showed only the barest reaction on accommodation, while later they showed a moderately good reaction. This relative diminution of reactivity on admission may be ascribed to the intoxication.

I have already stated that bromide psychoses usually clear up in from two to six weeks after discontinuance. We may plausibly suppose that a patient with paresis would, if anything, require longer than the average to recover from a bromide delirium, and therefore the recovery of our patient in only 10 days may at first glance seem puzzling. We must, however, remember that different people possess different degrees of innate resistance to delirium. Conceivably a person may have such strong resistance to delirium that even when his resistance is lowered by paresis it still exceeds that of the average individual. In other words, the fact that our patient recovered sooner than the average is no more puzzling than the fact that *some* men at 60 can outwalk the average man of 30.

VARIETIES OF BROMIDE PSYCHOSIS

Three varieties of bromide psychosis are known today. 1. *A state of mental sluggishness*, in which the patient thinks and acts with great difficulty, being at the same time well oriented and having no hallucinations. This state is commonly spoken of as a "simple bromide intoxication." 2. *Delirium*, in which the patient is disoriented, generally with restlessness, hallucinations, and a multitude of fears. (Disorientation is the one essential feature of delirium.) 3. *Hallucinosi*s, in which the patient has hallucinations, but is perfectly oriented.

It is possible that additional varieties will become known as time proceeds. Thus, psychiatrists are familiar with paranoid states which clear up a few weeks after the patient's admission to a hospital. It is possible that some of these transitory paranoid states, when studied in relation to the criteria here outlined, will prove to be symptomatic of bromide intoxication.

In practically all cases of bromide intoxication neurological signs occur. The commonest of these are irregularity of the pupils, and sluggishness in their reaction to light and on accommodation, tremors of face, tongue and fingers, thickness of speech, unsteadiness of gait and station, and diminution or exaggeration of the deep reflexes.

As a sample of the disorders on which bromide psychoses may be superimposed, the following data are cited. Among the 505 "first admissions" to the Harrisburg State Hospital during the two years beginning June 1, 1931, there were 15 unquestionable cases of bromide psychoses. Five of these patients had been given bromides because of a variety of neurotic symptoms, associated in some instances with abdominal, pelvic and other physical ailments, one because of herpes zoster, one because of worry over recently discovered hypertension, one because of an acute psychosis the

details of which are not clear, one because of a hypochondriacal depression developing on the basis of cerebral arteriosclerosis, one because of an excitement developing on the same basis, one because of early senile symptoms, one because of symptoms arising from general paresis (the case herein reported), one because of the after-effects of a concussion, and two because of epilepsy. Further details of eight of these cases may be found elsewhere.³

TREATMENT

An unsettled question is whether the abrupt discontinuance of bromides ever does harm. The aggravation of a few cases after discontinuance has led several authors to conclude that abrupt discontinuance is risky. In my earlier paper³ I endeavored to show that the evidence so far available does not make this conclusion obligatory. The current practice at the Harrisburg State Hospital is to discontinue bromides, and so far nothing has occurred to cast doubt on the wisdom of this procedure.

The patient should be kept in bed until the intoxication has subsided. Fluids should be forced. If there is no nephritis, four grams (one dram) of sodium chloride should be given thrice daily, the chloride ion facilitating the excretion of the bromide ion. Restless patients should be given continuous baths. The need of using only the least toxic hypnotics is especially urgent in patients with bromide intoxication, poisoned as they already are, for the majority of patients who require hypnotics, paraldehyde will suffice. Cardiac stimulants should be given when indicated.

PREVENTION

Bromides are useful medicinal agents. What renders them so often harmful is that the busy physician too hastily dismisses his neurotic patient with the advice, "Keep on taking that salty medicine, the same as before." The patient, as a result, may be taking bromides for many months before the physician is fully aware of it. When the nervous symptoms grow worse, the physician is apt to increase the dosage of the bromides, without duly considering the possibility that the aggravation is due to bromide poisoning. It is important to remember that bromides will accumulate in the body in inverse proportion to the amount of chlorides ingested, a person who takes little table salt will therefore develop a bromide intoxication with especial ease. Moreover a patient may be getting bromides from several physicians simultaneously, and may thus develop an intoxication from a multiplicity of cautious dosages.

The following suggestions are urged.

1. When contemplating the administration of bromides, the physician should seek to ascertain whether the patient is already getting bromides from another source.

2. The physician should know whether the patient takes much or little table salt. In the latter case he should be doubly cautious.

3 The physician should not relax his vigilance just because the dosage he is giving is one that has proved harmless in the majority of his patients.

4. When a nervous patient getting bromides grows worse, the physician should promptly discontinue the drug unless he has good reason to believe that it bears no responsibility for the aggravation.

5 When a patient has been taking bromides for a month or more, it is wise to discontinue them occasionally for a week or two. An occasional Walter-Hauptmann test is the best way to make sure that the patient is not becoming intoxicated.

SUMMARY

The following criteria establish the diagnosis of a bromide psychosis: 1 The existence of a bromide intoxication, as shown by the Walter-Hauptmann test. 2 The fact that the psychosis began after the patient had become intoxicated. 3 The fact that the psychosis clears up within a short time—generally from two to six weeks—after the discontinuance of bromides. (It is possible that in exceptional cases a bromide psychosis lasts much longer than six weeks after discontinuance.) It is important to differentiate a bromide psychosis from the underlying neurosis or psychosis on which it has been superimposed. An illustrative case is presented of bromide delirium superimposed on general paresis. The treatment and prevention of bromide intoxication are discussed.

REFERENCES

- 1 KATZFELBOGEN, S, AND GOLDSMITH, H. The hemato-encephalic barrier, diagnostic value of the bromide test in mental diseases, *Am. Jr. Psychiat.*, 1931, **x**, 1045-1055.
- 2 WUTH, O. Rational bromide treatment, new methods for its control, *Jr. Am. Med. Assoc.*, 1927, **LXXXVIII**, 2013-2017.
- 3 LEVIN, M. Bromide delirium and other bromide psychoses, *Am. Jr. Psychiat.*, 1933, **xii**, 1125-1163.

SUBACUTE BACTERIAL ENDOCARDITIS *

By J H MUSSER, M D , F A C P , *New Orleans, Louisiana*

THE FACT that I have seen in the Charity Hospital in New Orleans in the past two years many more cases of subacute bacterial endocarditis than I remember ever having seen in the past, has led me to review the history of 14 cases that I have observed in this period of time in order to present to you certain features of a disease which, in one section of the country at least, seems to be increasingly prevalent. Some years ago Blumer¹ wrote that "it is difficult to say whether the disease is actually increasing or whether there is merely an apparent increase due to increasing knowledge on the part of the profession to recognize the condition. Personal experience would rather favor the latter view." This may be true, but on the other hand it is rather doubtful that a sudden accession of knowledge should have come to the staff of the Charity Hospital in the last year, in which time as many cases of subacute bacterial endocarditis were recognized as in the previous 10 years. It was only a few decades ago that the disease was first recognized but since that time there have been innumerable communications in the medical press concerning it. Certainly as a result of the teachings of Osler, Janeway, Libman, Blumer and Lewis there is no excuse for any failure to recognize the condition because of lack of information. Libman says that "the disease is common", Lewis notes the same, the late Frank Billings, according to Blumer, had seen over 100 cases. Among the British soldiers studied by Lewis and his associates, at the concentration point for heart cases in England, it was found that approximately 8 per cent of sick soldiers who developed heart disease and were invalided home, had subacute bacterial endocarditis. These observations point to the relative frequency of the disease if looked for and if borne in mind.

In reviewing these 14 cases that I have seen in the last two years I wish to say that with one exception all of these patients were observed in the Charity Hospital. I wish, furthermore, to indicate that the expressions of this type of endocarditis are often extremely indefinite and vague. The symptoms are so protean in character that the possibility of such a condition as subacute bacterial endocarditis existing in the individual who has not had previous heart valve damage is often not considered until ultimately certain signs and laboratory findings develop which make the diagnosis unmistakable.

DURATION OF ILLNESS

Subacute bacterial endocarditis is separated from acute, bacterial, ulcerative or fulminating endocarditis by an arbitrary time period. Most phy-

* Read before the Montreal Meeting of the American College of Physicians, February 10, 1933

From the Department of Medicine, School of Medicine, Tulane University of Louisiana, and the Charity Hospital of Louisiana

sicians consider bacterial endocarditis extending longer than a period of two months as being subacute, or over a year as being chronic. In this group of patients the course of the disease was variable, extending from a period of slightly over a month to somewhat over a year. The rather protracted illness that occurs so frequently will be exemplified by the following case report.

CASE I

J. P., a man of 32, was taken ill slightly more than eight months before his death, his illness coming on quite suddenly with chills, and fever which rose to 102°. He improved but was left with residual weakness and fatigability. About a month after the onset he noticed that his heart occasionally skipped a beat. Gradually the patient went downhill and finally entered the hospital some six months before his death. At the time of admission to the hospital the most important physical observation was a rather harsh and loud systolic murmur heard over the mitral area and transmitted into the axilla. The pulmonic second sound did not seem to be accentuated and the heart was not enlarged. At the time of admission the leukocyte count was 7700, the red blood cell count was 4,395,000, the blood culture was positive for *Streptococcus viridans*. The urine showed nothing of moment. Repeated blood counts showed very little alteration in the total number of red cells and the same thing held true for the leukocyte count. The spleen was enlarged and during the months he was in the hospital was definitely tender on deep palpation. He also developed during the course of the disease tender finger tips and ultimately clubbing of the fingers. Petechiae were present over the hands and feet. All the time the patient was in the hospital the temperature ranged from subnormal to 101°-102°.

At autopsy small hemorrhages were found in the internal organs, the mitral valve showed many small vegetations which were not friable, the valve itself was not fibrotic. There was also a vegetative mass 4.5 cm. in diameter on the endocardium of the left ventricle. Healed infarcts were found in the spleen. There was a focal glomerular nephritis with healed infarcts of the kidneys. A small subarachnoid hemorrhage was also noted.

Discussion. This patient was ill for many months before the ultimate lethal termination. In most of our cases the illness was not so protracted. In many of them the patient died within a few months after the apparent onset of the illness. Seventy-five per cent of patients are said to die between the third and eighth months and our figures are in accord with this observation of Blumer's. In one instance the patient died a little over a month after being admitted to the hospital but I have no definite information as to the exact time his illness began.

A definite history could be obtained from the other cases and the story invariably was that they had been sick not for days but for weeks. However, only one of the patients survived the first year after the onset of the infection.

The following case, which is briefly abstracted, illustrates the fact that the clinical picture may suggest that the infection causing death is some other than subacute bacterial endocarditis.

CASE II

J G, aged 19 years, had been ill, with evidence of rheumatic heart disease, for two months prior to admission. He had had one previous attack of rheumatic fever some seven years before admission to the hospital. Since then he had had several attacks of heart failure and his condition had shown a gradual downhill trend. When he was admitted to the hospital his chief complaints were increasing weakness and shortness of breath. The examination at that time showed a well nourished, anemic appearing boy whose heart showed a diffuse apical impulse, together with an apical thrill, systolic in time. The heart was enlarged to the left 11.5 cm. A murmur was heard in the mitral area, and in the aortic area a rumbling first sound with a soft blowing second sound. The spleen could not be felt and no petechiae were found. He had the usual vascular phenomenon of aortic insufficiency, including a blood pressure of 130 systolic and zero diastolic. The urine showed a few red cells on several examinations. He had a relatively marked anemia, the red cells being 2,925,000. The total white count was persistently between 13,000 and 15,000. He ran a septic temperature throughout the course of the disease, and the *Streptococcus viridans* was found in the blood after the fifth culture. The diagnosis was made of rheumatic aortic regurgitation, and subsequent subacute bacterial endocarditis. He died apparently from heart failure rather than as a result of an infectious process.

Discussion In this instance the boy might well have had rheumatic heart disease in the acute phases were it not for the fact that his blood culture ultimately was found to be positive. He also gave a history of having had a petechial rash over his legs. Other interesting features of this case were involvement of the aortic valves, the long delay before obtaining a positive blood culture, and the limitation of direct evidence of embolic phenomena to the occurrence of a few red cells in the urinary sediment on several examinations.

BLOOD FINDINGS

There is a very general impression that the leukocyte count in subacute bacterial endocarditis is relatively high. Cotton,² of the Sobraow Military Hospital, in his considerable series of cases, found the average count to be 10,800. In the present series the count ranged from 4,000 to 65,000. Ten of the counts were under 11,000. In those patients in whom the count was frequently repeated there was a tendency for it to remain at approximately the same figure as the initial count. There were only two counts over 20,000, one of these was 65,000. Two counts fell between 11,000 and 20,000, one of 17,000, and one averaging around 14,000. The percentage of polymorphonuclears was in direct relationship to the increase in the total count. The counts showing practically normal figures also had a differential picture which was essentially normal.

Anemia is one of the characteristic features of the disease. In five of our patients the red count was under 3,000,000, in four it was under 4,000,000 and in four it was between 4,000,000 and 5,000,000. There were no extremes, such as the counts occasionally recorded in this disease, of less than 2,000,000 or over 5,000,000. The usual findings in our series may be illustrated by the following case.

CASE III

E. H., aged 24, was admitted to the hospital on account of shortness of breath and cough. His illness started three months before admission with, in his words, "severe chest cough." Since then the cough had remained constantly present with more or less acute exacerbations. He had had no hemoptysis and no chest discomfort or pain. He entered the hospital January 11, 1932. No history could be elicited of any symptoms in the past even suggestive of rheumatism or the rheumatic state. The heart examination showed a systolic thrill over the apex of the heart. The heart border extended 2 cm. to the right of the sternum, and 13 cm. to the left. There was heard a low, long systolic murmur at the apex transmitted to the axilla. There was a questionable presystolic whiff which had a vague sort of crescendo character. The liver was enlarged, the spleen was palpable and the lungs showed basal rales. This man had fever of 102° on admission which was maintained between 99° and 101° with a pulse rate of between 110 and 128 during all the time he was in the hospital. The blood count on several examinations showed an anemia with a red cell count averaging 3,100,000, and a corresponding reduction in hemoglobin, the leukocyte counts were 8,000 or under and there was no change in the differential formula. On both occasions that a blood culture was made, *Streptococcus viridans* was isolated. A roentgenogram of the chest was taken because of the physical findings of a solidification which suggested an infarct. This was confirmed by the roentgenogram. The diagnosis was made of rheumatic heart disease with mitral stenosis on which was engrafted subacute bacterial endocarditis. This was confirmed at autopsy which showed a markedly enlarged heart, the mitral valve was affected. It was found to be stenosed and thickened, and on the surfaces was a collection of pinkish red polypoid vegetations. One leaf had been ulcerated. The left and middle aortic cusps were thickened with several small polypoid vegetations on their surfaces. The lungs showed definite areas of infarction, while the spleen, which was enlarged, did not show evidence of infarction nor was there any found elsewhere.

BACTERIOLOGY

In our series of cases of subacute bacterial endocarditis, streptococci were isolated from the blood stream in the majority of instances. Libman has pointed out that the only two organisms of moment as responsible agents are the green streptococcus in 95 per cent of the cases, and *Bacillus influenzae* in the remaining 5 per cent. In Blumer's series of cases streptococcus is reported 248 times, 169 times it is specified as the *S. viridans*. Pneumococci were found 16 times in this series, *B. influenzae* 16 times, and other organisms only exceptionally. In addition to the frequently found green streptococcus it is not unusual to find other organisms. For example, Lenhartz³ found in a series of 37 cases one instance of *Staphylococcus aureus* and one of *Staphylococcus albus* endocarditis. Clawson⁴ in an analysis of 220 cases found seven instances of *Staphylococcus aureus* infection as contrasted with 34 of streptococcal origin. Stich,⁵ reporting on a case of subacute bacterial endocarditis due to *Staphylococcus albus*, states that next in order of frequency to the streptococcus comes *Staphylococcus aureus*, then pneumococcus and gonococcus and last of all *Staphylococcus albus*. There is apparently very little difference in the clinical expressions of the disease, when due to one or the other type of organism. Subacute bacterial endocarditis may in rare instances be produced by the meningococ-

cus Gwyn⁶ has reported on such a case. He states that there have been some few cases reported infected with this type of organism and gives references to seven such instances. Gwyn writes that there is "little deviation from the classic picture of subacute bacterial endocarditis." He advances as an explanation for the relatively large numbers of cases of chronic meningococcal septicemias that have been reported, the suggestion that they may represent an unrecognized meningococcal endocarditis. Recently Dickar⁷ reported two cases of *Bacterium acidilactici* endocarditis.

In the present series the positive blood cultures yielded only the *S. viridans*. In nine instances this organism was found by this procedure, in five cases the culture was negative though three of these five patients had definite bacterial endocarditis at autopsy. In the other two instances the organisms were not found and the patients did not come to autopsy but the clinical course of the disease was so characteristic that there could be little question of the diagnosis.

Considerable difficulty arises at times in growing the organism from the blood. In Case III just cited, that of E. H., organisms were isolated on two occasions in large numbers. In Case II, that of J. G., it was not until the fifth culture that a relatively profuse growth, 86 colonies per cubic centimeter of blood, was discoverable in the culture medium on the seventh day after withdrawal of blood. The difficulty at times in obtaining positive cultures is readily explicable because the green streptococcus is a slow grower, and the culture should be kept for at least 10 days before being discarded. It is advisable also to take considerable quantities of blood because frequently the counts may be as low as one to five organisms per cubic centimeter of blood.

TABLE I
Subacute Bacterial Endocarditis

Case No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Cardiac murmurs	+	+	+	+	+	+	-	+	+	+	+	+	+	+	13
Anemia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	14
Enlarged spleen	+	+	+	+	+	+	+	+	+	+	+	-	+	+	13
Petechiae	+	-	+	+	-	+	-	+	+	-	+	-	+	-	8
Tender or clubbed fingers	+	-	+	+	-	-	+	+	+	-	+	+	+	-	9
Other embolic phenomena	+	-	+	+	+	+	+	-	-	+	+	+	-	+	10
Blood culture	+	+	-	+	+	-	+	-	+	+	+	+	-	-	9
Leukocytosis	-	-	+	+	-	-	-	-	-	-	-	+	-	+	4
Hematuria	-	-	+	-	-	-	-	+	-	-	+	+	+	-	5
Previous arthritis	-	+	-	+	-	+	-	+	+	-	-	+	+	-	7

The case of A. B. represents the type of case in which the discovery of a positive culture of *Streptococcus viridans* makes possible the correct diagnosis in a patient with fever of undetermined origin.

CASE IV

A. B., a man of 50, was a big, strong, athletic type of individual. He was taken sick, about two months prior to the time he was first seen, with what was diagnosed as

grippe Up until that time he had been absolutely well, in fact two months before he had had a most thorough physical examination, at which time his heart was judged to be entirely normal Following this so-called attack of grippe he ran a slight degree of fever for many days He felt miserable and wretched but was able to work about half of the time Gradually the tiredness and weakness became so pronounced that he had to go to bed. Except for the fever, which was never very high, the physical examination revealed only a soft systolic murmur which was thought to be hemic Several blood cultures were negative In spite of the fact that he was gradually going downhill he showed nothing characteristic of any definite disease After an interval of several months, he developed almost simultaneously tender finger tips and a positive blood culture These two findings determined the diagnosis definitely From this time on the tender finger tips occurred at intervals, petechiae were subsequently observed and the spleen once was the site of an infarction The temperature, until the antemortem rise, was at no time over 101° The leukocyte count remained persistently under 10,000

Discussion In this instance none of the characteristic features of bacterial endocarditis were present except fever of unexplained cause until the tips of the index and middle fingers of the right hand suddenly one day became quite painful and tender and remained so for several hours Shortly after this the occurrence of a positive blood culture definitely showed that subacute bacterial endocarditis was present As the disease progressed more typical symptoms developed

NEPHRITIS

Baehr,⁸ among others, has stressed the importance of nephritis and other renal complications in subacute bacterial endocarditis due to anhemolytic streptococci He has called attention to the occurrence of acute glomerular nephritis and of chronic glomerular nephritis in 91 cases of subacute bacterial endocarditis Embolic glomerular lesions are found in many instances An interesting group is constituted of those cases, only occasionally seen, in which there occurs an absence of streptococci from the blood stream together with the findings of a diffuse glomerulo-nephritis It is in this group of patients that a true glomerular nephritis may be observed, whereas in the patients who have bacteria in the blood stream no evidence is found of diffuse glomerular nephritis The suggestion has been made by Baehr that the glomerular damage may be the result of phenomena concerned in the recovery from infections

In our series of cases there were five patients who showed red blood cells in the urine These patients were individuals who had streptococci in the blood stream and it was assumed that the red cells represented embolic occurrences in the kidneys This was confirmed in one of the postmortems in which definite renal infarcts were observed In two instances there was evidence of definite nephritis a focal glomerular nephritis in one case in which there were streptococci in the blood stream

The abstracted history of one of the cases, that of J P, already has been presented He showed no definite evidence of nephritis while in the hospital except for an occasional granular cast There was no fixation of spe-

cific gravity and for only a short time before his death was there any albumin in the urine. It is quite possible that the glomerular nephritis found at autopsy was one of long standing. A résumé of the history of P. D., the second case of nephritis, is as follows:

CASE V

This patient, aged 27, died one month after coming into the hospital. He had been perfectly well up to two years before his final illness but at that time he began to have arthritic symptoms such as pain and swelling of the elbows and knees. Six weeks before admission he caught a cold. The fever from which he was suffering, together with weakness and slight dyspnea on exertion, were the only subjective symptoms of moment aside from pain in the right ankle. The physical examination of this patient showed a heart which was slightly enlarged to the left. There was a diffuse, forceful, to and fro murmur in the aortic valve area. In the mitral area there was a systolic-diastolic murmur, and a presystolic thrill. The spleen was enlarged and hard. Repeated blood cultures were taken which were never positive. The urine had always a high specific gravity, quantities of albumin, occasional red cells and at one time the note was made that it was loaded with red cells. The leukocyte count varied between 3,000 and 8,000, polymorphonuclears being 73 per cent on an average. The blood chemistry was negative. The temperature in the hospital varied between subnormal and 101°, going over 100° only once, the pulse rate was never unduly rapid. At autopsy the heart muscle was found to be pale, flabby and with some dilatation of the left ventricle, which explained the slight cardiac enlargement. The aortic valves showed non-friable vegetations leading to marked disfigurement of the valves. A small vegetation was found on a leaflet of the mitral valve. The kidneys were enlarged, dark red in color with thickening of the cortical zone. Microscopically they showed marked changes in the glomeruli with dilatation of the loops of the glomeruli. The tubules were also swollen.

Discussion. The diagnosis in this case was in no way difficult. The patient had petechiae on his chest when he was first seen and subsequently had crops of them from time to time. His finger tips were clubbed, he had well marked anemia. The murmurs were thought to be due to a preëxisting rheumatic endocarditis but the autopsy findings indicated that it is quite possible that the lesion was entirely the result of the bacterial endocardial involvement. There was no question concerning the diagnosis of the existing nephritis, a nephritis which occurred in the patient who had, as Baehr noted, no streptococci in his blood stream after many cultures and who apparently was in the stage of recovery from the infection. His death was due to a combination of the heart and kidney condition rather than to the infection. During the last 10 days of the patient's life the temperature was never over 99°, yet he suffered from well marked cardiac failure.

SPLEEN

Enlargement of the spleen was an almost invariable finding, it occurred in 92 + per cent of the cases in this series. Six of these patients had definite infarctions in the spleen. As a matter of fact, infarction of the spleen seemed to be more common than any other embolic phenomenon except skin petechiae. The occurrence of splenic embolism and the characteristic pain that it produces are exemplified in the following case:

CASE VI

D P, a young colored woman, 19 years of age, came into the hospital November 22, 1931, complaining of pain in the left side of the abdomen and fever. The fever had been present for about three weeks. With it there was an occasional chill and the usual symptoms associated with fever. One week before she came into the hospital she had a sudden severe, sharp pain in the abdomen which has persisted. This pain was relieved by sitting up in bed. The pain and fever were the main symptoms. At the age of 14 this woman had arthritis which involved both knees and she has had recurrent attacks of tonsillitis. The important physical finding in the heart was a diffuse apex beat 9.5 cm. to the left of the midline, the right border of the heart was not enlarged. At the apex there was a soft systolic murmur which replaced entirely the first heart sound. The laboratory findings showed a red cell count of 3,900,000, and a total white count of 8,750 of which 78 per cent were polymorphonuclears. Blood cultures demonstrated a *Streptococcus viridans* infection. The temperature was occasionally up as high as 101° but the pulse rate was never unduly accentuated. The patient deserted and was re-admitted again February 14, 1932. In the interim the only occurrence of moment was a repetition of the severe, sharp, agonizing pain in the region of the spleen which came on during the bus ride to her home. On this admission the condition was worse than it had been. The systolic murmur had become much intensified, the spleen was further enlarged and the red cells had fallen to 2,400,000. This patient, several days after admission, suddenly developed a squint and ptosis of the left eye. Spinal puncture showed nothing. During a stay of several weeks in the hospital temperature was somewhat higher than on the previous admission. The patient again insisted on leaving.

Discussion In this instance there is a clear-cut definite history and observations of the phenomena of embolic involvement of a splenic vessel. The pain as described in the above history was variable in its persistency as it usually has been in other cases. It may last only a few hours or again may persist for some days. Apparently the infarcts of longer duration must extend out to the periphery of the spleen and set up a definite perisplenitis. In several other instances there was evidence of involvement of the splenic capsule and in one case it was thought that a friction rub could be heard.

There is considerable variability in the size of the spleen. The splenic tumor of infection is not a greatly enlarged organ but can be definitely palpated, and is soft and painless. On the other hand, as shown by autopsy, in two instances the spleen was much more enlarged than would occur from simple infection alone. A sensation of hardness or induration on palpation was characteristic of the spleen, which was the site of infarcts.

VALVES INVOLVED

The occurrence of previous arthritis with endocarditis determines to a certain extent at least the location of the vegetative process of subacute endocarditis. In seven instances a clear-cut definite history was obtained of a previous rheumatic infection. In five instances there was no story which could remotely indicate a previous infection of rheumatic nature. In two cases it was believed there was congenital heart disease, because the valve apparently involved was the pulmonic*. The previous rheumatism in all

* At the present time there is a patient in the Charity Hospital with subacute bacterial endocarditis on a patent ductus arteriosus.

instances, except two, had caused injury chiefly to the mitral valve. In two instances the aortic valve was undoubtedly the one predominantly affected. It is a nice question as to whether or not the valvulitis of rheumatic fever is confined to one valve alone in most cases. Seven of our patients had evidence of both aortic and mitral disease. Of these seven, one was purely an aortic lesion with a minimal involvement of the mitral valve. In another instance the preexisting valvular lesion was the typical mitral stenosis of rheumatic heart disease and the aortic lesion was questionable.

One of the interesting features of this disease is the fact that subacute bacterial endocarditis develops in an abnormal heart, and that the abnormality is either rheumatic valvular disease or some congenital defect. Very rarely indeed does it happen that valves, the seat of syphilitic disease, become secondarily infected with the green streptococcus, and the same may be said of the sclerotic valves of senescence. The occurrence of a superimposed bacterial endocarditis on syphilitic aortic endocarditis is so exceptional as to merit recording. Craven⁹ reported such a case and in reviewing the literature found 11 further reports but discarded most of them as being based on evidence insufficient to substantiate the diagnosis.

The determination of the location of the primary infective lesion or the location of the most severe active endocarditis is difficult, in fact impossible. In three instances the mitral valve alone was affected and in these three instances the patient apparently had never had any previous heart damage. The evidence of mitral valve involvement consisted of a soft, blowing systolic mitral murmur without evidence of heart enlargement or of any of the findings of prolonged or chronic valvular heart disease.

That it is impossible dogmatically to state that such and such a valve is the chief one affected is proved by our autopsy experience. In one instance the vegetative processes involved only the auricular wall but in this patient no cardiac murmur was audible. Evidently healing had taken place after the valve was affected, if it was, and no evidence of infection could be demonstrated grossly. Incidentally mural endocarditis is relatively common. Particularly interesting in this connection is a case report in which we thought that engrafted upon a congenital heart lesion was a subacute bacterial endocarditis. Before reciting this case history it might be said we had one other case in which the findings were typical of congenital heart disease but which we were unable to prove at autopsy.

CASE VII

O. C., a young white woman, 19 years of age, had been sick for three weeks prior to admission to the hospital. One month previously she had had a tooth extracted and a week later had fallen ill with high fever and chills. She was thought to have typhoid fever, the continued fever was the only symptom of note. She had had no other severe sickness in the past. We were unable to obtain any information at all suggestive of a congenital heart lesion.

The physical examination pointed distinctly to a low grade congenital pulmonic stenosis. Aside from the anemic, pasty appearance of the patient the only important

findings were in the heart, which showed a slight enlargement to the right. The first sound over the pulmonic area was distinctly accentuated. There was a loud, blowing diastolic murmur over this region and a softer, lower pitched systolic at the base of the heart, highly suggestive of congenital pulmonic stenosis. This patient rapidly went downhill and died some 10 days after admission to the hospital. During her stay in the hospital petechiae were observed on the buttocks. The spleen was found to be slightly enlarged and the leukocyte count ranged between 22,000 and 23,000, polymorphonuclears 80 per cent. The temperature was of the typical septic type. Four blood cultures were negative. At autopsy a slight enlargement of the spleen was noted and several small areas of infarction in the kidney (on one occasion red cells were found in the urine). Otherwise the chief findings were in the heart. The heart showed enlargement of the right ventricular wall which was approximately as thick as the left ventricular wall. The pulmonic cusps were thickened irregularly and narrowed. They were not fused and showed no vegetations. Two centimeters above the valve there was found a small vegetative growth measuring about 0.5 cm in diameter and an interval of 1 cm of normal artery separated a second vegetative area which was somewhat larger than the other, measuring about 1.5 cm in diameter.

Discussion. This case was of unusual interest on account of several very interesting possibilities. Our original concept was that a bacterial endocarditis had been superimposed upon a preexisting congenital heart lesion. This idea seems dubious in view of the fact that the valve cusps were thickened and irregular as if a chronic inflammatory process had involved them some time in the past. These autopsy findings would seem to discount the congenital origin of the lesion. Particularly to be emphasized is the fact that this girl, who was a school teacher, had had her heart examined more than once and had always been told it was normal. It seems more logical to assume that healing and reparative processes had covered and obliterated the vegetations on the valves but had not yet occurred in those situated higher up on the wall of the artery. Another possibility is that the girl might have had a bacterial endocarditis previously and that the final illness was a second attack as a result of the entrance of green streptococcus into the blood stream, the infection entering after the abscessed tooth was extracted.

Lewis and Grant¹⁰ have reported on bicuspid aortic valves in infective endocarditis. They write that it is theoretically possible for normal valves to be converted into the bicuspid valves which are found at autopsy. Lewis states that "until we could deny that subacute infective endocarditis is a process capable of complete healing—and we are not yet in a position to enter upon such a denial—the possibility had to be borne in mind that certain instances of bicuspid valve, found apart from active endocarditis, might be the healed products of such an infection long since cured." Subacute endocarditis may have a long duration. It is rather difficult to conceive of the valve with its vegetations remaining unchanged over a long period of time. These vegetations may become scar tissue and represent commissures, ulcerated and subsequently healed and retracted. In view of these statements of Lewis', might it not be presumed that in this particular instance the pulmonic valve had been involved months previously and the endocardial lesion

had become quiescent, either completely cured or else remaining as a small locus on the artery to become reactivated under the influence of infection at the time the tooth abscess existed

Here it might be appropriate to comment on subacute bacterial endocarditis occurring after tooth extraction. A review of the literature of the last several years shows a general recognition of the fact that the possible appearance of subacute bacterial endocarditis after the extraction of a tooth or of teeth is a definite hazard to be feared. Bernstein¹¹ reports the development of a fatal subacute endocarditis in a young man within five days following the extraction of a tooth. Brown¹² reports another such case. Recently, within the last six weeks, I have seen in consultation an old gentleman dying from an acute endocarditis, the symptoms of which came on about one week following the extraction of half a dozen infected teeth. The disease may follow other operative procedures on streptococcic foci. Abrahamson¹³ reports a case of subacute bacterial endocarditis following the removal of tonsils, as well as two others in which it followed the extraction of teeth. This author stresses the fact that evidence such as this would tend to prove that the organisms of subacute bacterial endocarditis may come from the teeth or tonsils. Under any circumstance, the many reported occurrences of the disease after measures to remove foci of infection indicate that extreme precautions should be taken when such foci are eradicated by surgical procedures in patients with preexisting valvular disease.

According to Lewis not only are there instances of recovery from subacute bacterial endocarditis but it is remarkable in some cases how little effect its presence may exert upon the heart. In this conjunction it is of interest to note the report of a case of a woman who died suddenly as a result of involvement of the right and left coronary arteries by vegetations which obstructed the blood supply to the heart. In this instance the patient had apparently been entirely well up to the time of her sudden death and was not even cognizant of the fact that her heart was affected or that she had had a recent infection¹⁴. In discussing atypical initial symptoms Mallory¹⁵ mentions cases presenting the clinical symptoms and signs of Raynaud's disease, and others having appendectomy performed for what turned out to be an intestinal embolus.

EMBOLIC PHENOMENA

The most definite, positive, substantiative finding is the occurrence of embolic phenomena. I have already noted the occurrence in this series of red cells in the urine in five instances, indicating the presence of renal emboli. Outstanding embolic symptoms occurred in five instances in the spleen. In one case, D. P., already mentioned in detail, the occurrence of squint and ptosis of the eye indicated cerebral embolus. A subarachnoid hemorrhage was found at autopsy in the case of J. P. Five of our cases showed very definite tender fingers, the nodes of Osler, transient painful areas of redness in the finger pads. None of them exhibited splinter hemorrhage under the

finger nails as described by Blumer. Retinal hemorrhages or subconjunctival hemorrhages were never seen. In eight instances petechiae were definitely observed on different parts of the body. In two instances gross vascular lesions occurred which were quite spectacular. In one instance, a boy, in fairly good condition despite the bacterial endocarditis, had a sudden hemorrhage from the mouth and promptly died as a result of the blood loss. In this instance the bleeding was probably due to an embolic or mycotic aneurysm although no evidence that such existed was discoverable before his death. Unfortunately there was no autopsy. This boy was the youngest of our group of patients, being only 13 years of age.

CASE VIII

The most spectacular case of vascular occlusion occurred in the instance of C H, the oldest of our group, a white male aged 57. He was in the hospital for two and a half months. His chief complaint was weakness and shortness of breath, both of which had been gradually progressing for a period of two years although he was not advised to stop work until shortly before admission to the hospital. He came into the hospital because of acute, severe pain in the upper part of the abdomen. The physical examination showed a man considerably emaciated. He was extremely dyspneic and had other significant findings of congestive failure. The heart border was 12 cm to the left of the midsternal line and the sounds were poor in quality and rapid. No murmurs were audible. The radial arteries showed no signs of gross arteriosclerosis. The spleen was decidedly enlarged and very tender. The patient ran a septic temperature during his stay in the hospital. Three days before his death he had severe pain in his arms with disappearance of the radial pulse on both sides, a quite remarkable coincidence. The fingers of the left hand and thumb of the right hand rapidly became bluish-black in color and gangrene set in. Laboratory examinations were as follows: the urine showed no red cells, the hemoglobin was 50 per cent, red cells 2,500,000, leukocytes 4,500, 69 of which were polymorphonuclears. At the autopsy two days later emboli were found in both of the radial arteries. There were vegetations (2 × 4 cm) amidst the papillary muscles of the left auricular wall. Polypoid vegetations were found on the mitral valve and on the aortic valve. The spleen showed evidence of numerous infarcts as did the kidneys.

Discussion This patient was apparently dying of congestive heart failure. The immediate cause of death, or better the actual accident that terminated the life of a man already near death was the occurrence of the emboli in the arms and in the spleen. This cardiovascular accident was just enough to be fatal.

Evidences of involvement of the lung by emboli were found twice at autopsy. In one instance, that of E H, already quoted, the lungs showed rather extensive evidence of infarction but no evidence of emboli causing hemorrhagic infarcts were found elsewhere in the body, a rather interesting observation in view of the fact that the right heart was entirely normal and that such pulmonary emboli must have come from some unrecognized area of thrombosis of a peripheral vein. In the instance of O C, right endocardial involvement was found but there were no areas of infarction other than those in the spleen and kidneys.

SUMMARY

The clinical data of a group of patients who died from subacute bacterial endocarditis are reviewed. For the most part this group adhered ultimately to the more or less classical, clinical features of this disease. Eleven of them were under 30 years of age, seven definitely had had a previous arthritis of rheumatic origin. Nine of them had positive blood cultures. All of them had anemia of various grades and all of them showed embolic phenomena of various types. One rather odd feature is that in one instance no murmurs were heard despite repeated efforts to observe these particular physical signs.

CONCLUSIONS

In this present series of cases it is true that ultimately and eventually the correct diagnosis was obtained but it was obvious that often the diagnosis may be in abeyance for weeks before definite clinical phenomena are exhibited which will determine positively the presence of subacute bacterial endocarditis in patients sick with fever over a long period of time. No conclusion can be drawn as to the apparent increase in the occurrence of this disease other than it is reasonable to suppose that the disease is more frequent than it used to be.

REFERENCES

- 1 BLUMER, G. Subacute bacterial endocarditis, *Medicine*, 1923, 11, 105-170
- 2 COTTON, T. F. Observations on subacute infective endocarditis, *Brit Med Jr*, 1920, 11, 851-854
- 3 LENHARTZ, H. Über die septische Endocarditis, *München med Wchnschr*, 1901, xlviii, 1178-1180
- 4 CLAWSON, B. J. Endocarditis, with special reference to subacute bacterial type, *Arch Int Med*, 1924, xxxiii, 157-184
- 5 STICH, B. Subacute bacterial endocarditis due to *Staphylococcus albus*, report of case, *Arch Int Med*, 1932, xlix, 666-670
- 6 GWYN, N. B. Subacute meningococcal endocarditis, *Arch Int Med*, 1931, xlviii, 1110-1117
- 7 DICKAR, L. Acute bacterial endocarditis due to *Bacterium acid lactici*, *Arch Int Med*, 1932, xlix, 788-798
- 8 BAEHR, G. Renal complications of endocarditis, *Tr Assoc Am Phys*, 1931, xli, 87-95
- 9 CRAVEN, E. B., JR. Syphilitic aortic endocarditis and superimposed bacterial (*Streptococcus viridans*) endocarditis, *Am Jr Path*, 1932, viii, 81-90
- 10 LEWIS, T., and GRANT, R. T. Observations relating to subacute infective endocarditis, note on normal structure of aortic valve, bicuspid aortic valves of congenital origin, bicuspid aortic valves in subacute infective endocarditis, *Heart*, 1923, x, 21-99
- 11 BERNSTEIN, M. Subacute bacterial endocarditis following extraction of teeth, report of case, *ANN INT MED*, 1932, v, 1138-1144
- 12 BROWN, H. H. Tooth extraction and chronic infective endocarditis, *Brit Med Jr*, 1932, 1, 796-797
- 13 ABRAHAMSON, L. Subacute bacterial endocarditis following removal of septic foci, *Brit Med Jr*, 1931, 11, 8-9
- 14 WEST, G. L. Sudden death in case of asymptomatic subacute bacterial endocarditis, *New Eng Jr Med*, 1931, ccv, 675-678
- 15 MALLORY, T. B. Aortic regurgitation beginning at the age of fifty years in a man who suffered from attacks of unexplained fever, *New Eng Jr Med*, 1932, ccvi, 1214-1217

THE RÔLE OF DESENSITIZATION IN RECOVERY FROM BACTERIAL INFECTION *

By W B WHERRY, *Cincinnati, Ohio*

OUR CONCEPTION of what goes on during infection and recovery is bound to undergo a change from time to time, for our knowledge of biological processes is always incomplete and we are being perpetually subjected to the influence of new discoveries. The hypothesis I am going to present to you when carried to its logical conclusion is not clear in all its details, but it has directed us in our experimental work and has brought forth results which will aid us in combatting bacterial infections.

An important factor in susceptibility and immunity, and one that largely has been overlooked, is that it is requisite in order for bacteria to thrive and multiply that they have food in solution. Since there is little or no free water in the colloids of normal tissue cells, bacteria must be able to put the colloids into solution—either through direct ferment action or by producing substances which are capable of hydrating colloids, or substances which when split by body ferments will yield tissue hydrating substances. In all probability some of these substances are amines. Since the known "soluble toxins" of bacteria require an incubation period after injection before their toxic action is manifested, it seems probable that the real toxin is not present in what we have been calling toxin but is liberated when a pretoxin is digested by body ferments. If an animal is possessed of ferments capable of splitting off toxic material from a pretoxin, that animal is susceptible, if an animal possesses ferments which are unable to digest a pretoxin, or if the split products are non-toxic, that animal is immune. Other factors are important in determining the relationship between parasite and host but I believe the factors concerned in tissue hydration deserve more consideration than they have received in the past.

Presenting the thesis in a different way—a microorganism can lead a parasitic existence only if it is provided with ferments which can act on the food substances provided by a host, if it can thrive at the low oxygen tension found in living tissues, if it can put the gels of the host into solution. If after implanting itself in the tissues of a host the interaction between the parasite and the host leads to the liberation of substances which injure the host and interfere with the normal defense mechanism of the host, then the parasite is a pathogenic parasite. Tissue hydration is detrimental to the normal defense mechanism because the local edema dilutes the antibodies, immobilizes the phagocytes and furnishes food in solution for the bacteria. While it is true that toxic substances may be localized for a time at the site of reaction, this results in many instances in local necrosis of fixed tissue cells. Other evidence that edema is an extremely important factor in in-

* Read at the Montreal Meeting of the American College of Physicians February 6, 1933

fection is shown by the fact that if at the beginning of an infection the tissues are strongly dehydrated the infectious process is brought to an end

Tissue hydrating substances are produced by bacterial ferments from suitable media. They may be liberated by autolysis of bacteria, or through the action of body ferments upon the bacterial protoplasm or products. It is through the action of such toxins that the phenomena of inflammation are produced.

In the sensitized animal the ability to split a specific protein is greatly enhanced and the phenomena of ordinary inflammation are greatly exaggerated and altered in certain directions. Here the reaction between parasite and host leads to very marked local edema. In many infections, tuberculosis, glanders, diphtheria, scarlatina, undulant fever, tularemia, one can demonstrate easily that the host is acutely sensitized by injecting a minute quantity of the specific antigen intradermally. I believe that further investigations will reveal the fact that in every case of infection the host is either already sensitized or becomes sensitized soon after infection. Some infections are uniformly accompanied by marked hypersensitivity, e.g. glanders, tuberculosis, undulant fever, tularemia. In a disease like tularemia of the ulcero-glandular type, where it is possible to determine the exact time when a patient lacerated his finger with the broken bone of a rabbit, and therefore just when infection occurred, Lee Foshay¹ has found that the patient is acutely sensitized at least as early as the third day after infection.

The degree of hypersensitivity manifested by different hosts infected with the same germ may vary considerably. In cases infected with *Staphylococcus pyogenes* one may encounter skin reactions of moderate degree or of very violent degree (marked congestion and edema, chills and fever, adenitis, local necrosis of skin).

When a sensitized animal is reinfected with the microorganism which produced the sensitivity this superinfection runs a course modified by the phenomena of anaphylaxis. Many of the objective manifestations of infectious diseases occur only after superinfection. In his work on the production of yaws in monkeys Otto Schöbl² was able to produce some of the later clinical manifestations, as seen in man, only when he practiced superinfection in sensitized animals.

There is an increasing amount of evidence to show that hypersensitivity to foreign proteins other than bacterial—pollens, foods, emanations, etc.—may favor infection. Shock to one bacterial protein may lower resistance by creating conditions which favor invasion by another species. Bull and McKee,³ during their studies on spontaneous respiratory infections in rabbits, made the following interesting observation: rabbits recovered from pneumococcus infection were found to be hypersensitive. Such rabbits were made "carriers" of *B. leptisepticum*. Now when a homologous pneumococcus autolysate was instilled into the rabbit's nostrils they developed local anaphylactic shock and this was followed in a few hours by an infection.

THE FAMILIAL INCIDENCE OF PEPTIC ULCER *

By HERMAN H RIECKER, M D , F A C P , *Ann Arbor, Michigan*

CLINICIANS have taught for a number of years that gastric and duodenal ulcers occasionally occur in more than one member of a family, but the fact never has received recognition in the American literature, nor is it generally considered in discussions concerning the etiology of the disease Stewart's¹ recent studies indicate that about 10 per cent of the population have ulcer at one time or another, and that while only about 5 per cent of ulcers become cancerous, in his series 16.8 per cent of gastric cancers arose in simple ulcers. Considering these figures, the familial incidence of the disease becomes of importance from the standpoint of the diagnosis and of the control of both conditions.

In 1897, Dreschfeld² noted the presence of ulcer in six families. In two instances, mother and daughter suffered with it, in one, father and daughter, in two, two sisters, and in one, a brother and sister. In 1907, Huber³ described 30 instances and from his experience gave the incidence of familial ulcer as 15 per cent. In these 30 families there were 80 cases of ulcer, and 10 of cancer of the stomach. In 1910, Czernecki⁴ published the history of a family in which a mother, son, and three daughters had peptic ulcer. Plaut,⁵ in 1913, found a family history of ulcer in 22 per cent of 50 cases of ulcer. Verbrycke,⁶ in 1915, reported two families, in one of which the mother, two sons and a daughter had peptic ulcer, the children's cases being confirmed by operation, while in the second family the mother died of cancer of the stomach and a daughter had ulcer. A case of ulcer was recorded by von Plitek,⁷ in 1914, in which a history was given of a brother and two cousins who had been operated upon for ulcer.

Spiegel's⁸ paper, published in 1918, contained a complete survey of 121 cases of peptic ulcer compared with 200 control cases distributed as follows:

	Family History of Ulcer	Family History of Cancer of Stomach
Ulcer patients 121	26.4%	14.8%
Control cases 200	5.5%	2.5%

A. F. Hurst,⁹ in 1921, drew special attention to the subject by describing six families in which ulcer had occurred in more than one member. In reviewing the literature at this time he quoted Strauss¹⁰ as having stated that in patients having ulcer, a family history of gastric disorder was obtained in one-third of the cases, while in non-gastric conditions such a history could be obtained in only one-twentieth of the cases.

In 1913, Dauwe¹¹ reported eight cases of ulcer with a family history of

* Received for publication December 23, 1932.

From the Department of Internal Medicine, University of Michigan.

the same condition. The incidence of ulcer was distributed among these patients' relatives as follows: the father had ulcer in four instances, the mother in four instances, a brother twice. Two relatives were affected in two of the cases. Dauwe believed the ulcer tendency to be inherited chiefly from the mother, and that a neurotrophic theory best explained the mechanism. This theory has been expounded by Mathieu and Moutier¹² and more recently by Draper¹³. Dauwe insisted that the neurogenic factor was primary in the causation of ulcer and that gastric hypersecretion was a secondary effect, a theory to which Bloomfield¹⁴ emphatically subscribes.

In 1925, Huddy¹⁵ reported two families, in one of which the mother and four sons had peptic ulcer, while in the other the mother had a cancer which had developed from an earlier ulcer, and her son had a duodenal ulcer. These cases were proved by operation. Wilkie,¹⁶ in 1927, stated "There would appear to be an undoubted hereditary tendency to ulcer, particularly in females. I have had to deal with two families in each of which three sisters had to be operated on for duodenal ulcer."

Menasci,¹⁷ in 1930, described the histories of two brothers, 39 and 31 years of age, both having ulcers in the prepyloric region. The father of these patients had died of carcinoma of the stomach, an uncle had died of perforated ulcer, an aunt had been operated on for ulcer, and another aunt had stomach trouble and nervousness. Menasci reviewed 71 cases of ulcer, 51 in men and 20 in women. There were 12 cases of cancer of the stomach in the families of these patients and an incidence of familial gastric disease (probably ulcer) of 26.7 per cent. He quoted Polacco who found an incidence of cancer of the stomach in ulcer families of 19.7 per cent. Menasci's results are in contrast to those of Ruhmann¹⁸ who found a history of familial gastric disease in 48 per cent of 50 ulcer cases, and of Grote who found evidence in 60 per cent. They compare well with the figures of Britt,¹⁹ which are 25 per cent, of Plaut,⁵ 22 per cent, and Zisa,²⁰ 33.3 per cent.

In 1923, Aschner²¹ reviewed the subject, incorporating Spiegel's cases, and adding 132 cases of her own with 200 controls, with the following results:

	Family History of Ulcer	Family History of Cancer of Stomach
132 ulcer cases	12.7%	9%
200 control cases	4.5%	1.5%

I have reviewed the clinical charts of 942 duodenal ulcer cases, diagnosed at the University Hospital over a period of five years. All charts were accepted which contained a family history, and about which there was no reasonable doubt as to the correct diagnosis. Confirmation by roentgen-rays had usually been obtained. In such a review, I was obliged to accept the family histories as such, and the proportion of cases giving a positive family history of ulcer is lessened considerably by fragmentary or inaccurate information. However, many of the histories were taken by senior medical

students and were quite detailed. All of them were checked by a member of the staff, and in probably none was the questioner consciously attempting to elicit a history of ulcer. There was exhibited considerable keenness to find evidence of cancer in the family, and I attributed this to the influence of the teaching of the late Aldred Scott Warthin²⁴ whose opinions concerning this subject are well known.

A history of "symptoms similar to my own" by the patient was considered sufficient evidence of ulcer to be included, because duodenal ulcer gives a constant and rather striking history not easily confused with functional disease. The greatest sources of error in this study lay in the fact that many patients have no clear memories of family illnesses, that the number of living adults among the siblings could not be taken into consideration, and that many times a part of the family history was noted simply as "negative." All such histories had to be included in the total number because any selection would favor a higher percentage of ulcer families.

The data are compiled under two headings: (1) a history of ulcer in parent or sibling of the patient, and (2) a history of cancer of the stomach in either.

TABLE I

Distribution of Ulcer and Cancer in the Families of 121 Cases of Duodenal Ulcer as Recorded in the Histories

Grand-father		Grand-mother		Father		Mother		Brother		Sister		Uncle		Aunt		Total	
U	Ca	U	Ca	U	Ca	U	Ca	U	Ca	U	Ca	U	Ca	U	Ca	U	Ca
2	2	0	1	30	20	14	4	50	1	15	1	3	6	1	1	115	36

Ulcer—U
Cancer—Ca

DISCUSSION

In the series of 942 cases of duodenal ulcer there was a family incidence of ulcer or cancer, or both, in 124 cases, or 13.0 per cent. The diagnosis was indeterminate in three cases and these were omitted in a study of the distribution among the relatives, as shown in table 1. A history of cancer of the stomach in a relative was obtained in 20 per cent which is not far from the general incidence as given by Stewart and Spiegel. However, in 121 cases of duodenal ulcer there was a family history of carcinoma of the stomach in 36 cases.

All cases of peptic ulcer are not of a familial nature, but from this study it would seem that in those with a positive family history at least one-third of the families will show a death from carcinoma of the stomach. This phase of the subject was studied by Ernst Spiegel in 1918 who found a positive family history of stomach disease in 74 of 121 cases of peptic ulcer. In these 74 cases, carcinoma of the stomach occurred in 18, or about one-fourth of the families.

Both Spiegel⁸ and Bauer²² think that ulcer is four times more common

in the families of ulcer patients than in those of the controls, and that cancer of the stomach is six times more prevalent in the ulcer families

The problem could be approached by finding the frequency with which ulcers occur in the families of cancer patients. In a series of 31 such cases I found three families in which ulcer occurred, giving about the same percentage incidence as was obtained by studying the ulcer cases alone.

The results may be discussed with regard to the viewpoints that (1) cancer is inheritable as an organ-predisposition tendency, and (2) that cancer is engrafted on the site of ulcer in the stomach. This study could be interpreted in favor of the view that it is the tendency to ulcer which is carried in the family strain, and that the organ predisposition to cancer is on the basis of the occasional tendency of gastric ulcer to become cancerous. Any other interpretation would fail to explain the intermingling of the two diseases in the same family. A thorough study of the family history in cases of cancer proved to be engrafted on an ulcer might be of value in this connection.

An interesting example of the relation of ulcer to cancer in the same family is the following. In 1925, a man, aged 54, having been unsuccessfully treated by medical measures for a large gastric ulcer which had been present for six years, was referred for operation. Dr. Hugh Cabot found a large ulcer on the posterior wall of the stomach and, after removing a piece for pathological study, was obliged to cauterize it on account of its position. The pathological diagnosis was cancer on an ulcer base and the patient died two years later. In 1932, a younger brother of the above patient, aged 47, came to the hospital giving a typical history of duodenal ulcer, the diagnosis being confirmed by roentgen-ray.

A multiple incidence of ulcer in the family occurred 16 times in my series. The following case is an example of this tendency. A man, aged 29, entered the hospital in 1921 where a gastroenterostomy was done for duodenal ulcer. After numerous recurrences he was admitted again in 1931, when the following data were obtained. The patient's father had peptic ulcer, a brother had died of it at the age of 49, one other brother and two sisters of the six siblings have peptic ulcer, making six cases in this family in the two generations. The father was of English, and the mother of French-Canadian descent. The father was "nervous," the mother an epileptic, and the patient had several stigmata of psychoneurosis.

This study confirms the general impression that peptic ulcer commonly occurs in families, but so do other non-allergic diseases, such as gall-stones, rheumatic fever, cancer, and diabetes. We do not know the etiology of ulcer but, as in other diseases, the familial occurrence offers an unexcelled opportunity to study comprehensively such factors as the environment, food habits, constitutional type, and psychological pattern of the patients, all of which have been suggested as of etiological importance.

The inheritance of ulcer from the mother as emphasized by Dauwe was not prominent in this series, since there were only 10 ulcer cases in women.

In my series there was a father-son incidence in 47 cases, a mother-daughter relation in two cases, a mother-son relation in 15 cases, and father-daughter relation in 3 cases. However, in the cases reviewed from the literature, Dauwe's observation is, at least, partially substantiated, particularly by the reports of Huber and of Huddy.

The low percentage for the familial incidence of ulcer in this series is difficult to explain on any other basis than that the examiner was conservative in, or careless regarding, the importance of the family history. The incidence in a carefully worked out series should approach 30 per cent of the total cases on the basis of the data found in the literature, and of my personal experience with the disease.

Bauer and Aschner²³ have discussed at length the possible constitutional factors involved in the inheritance of ulcer and conclude that there is a recessive predisposition to the disease. They are in disagreement with Zisa²⁰ and Czernecki,⁴ who believe there is a very distinct constitutional type, the asthenic build, which predisposes to ulcer and which in turn is, of course, inherited. Bauer and Aschner could find no distinct type of body build characteristic of their cases.

If we accept the opinion of Zisa that the asthenic constitution is particularly predisposed to ulcer, and consider also the frequent coincidence of ulcer and hysteria, we may put forward the hypothesis that it is in those families in which asthenic builds and neurotic traits are common that a high incidence of ulcer will be found. In my series there was a clear example of such a family, the grandmother, mother, aunt, and daughter, all were of an asthenic build and highly neurotic. Each had a definite history of ulcer. The daughter and the mother are our patients, and the aunt is a patient in a nearby hospital.

CONCLUSIONS

In 942 duodenal ulcer cases there was a family history of ulcer in 13.0 per cent. In 121 cases having a positive family history, the familial incidence of carcinoma of the stomach was 33 per cent.

There is a familial incidence of peptic ulcer in upwards of 30 per cent of the cases reported in the literature, which strongly supports the constitutional viewpoint of the etiology of the disease.

The incidence of carcinoma of the stomach in families with a history of ulcer is considerably higher than in the general population.

BIBLIOGRAPHY

- 1 STEWART, M. J. Precancerous lesions of alimentary tract (Croonian lecture), *Lancet*, 1931, ii, 565, 617, 669.
- 2 DRECHSEL, J. Ulcer of the stomach in *A System of Medicine*, by many writers, edited by Sir Clifford Allbutt, 1897, Macmillan Company, New York, iii, p. 520.
- 3 HUBER, A. Über die Heredität beim Ulcus ventriculi. *Munch. Med. Wchnschr.*, 1907, liv, 204-207.

- 4 CZFRNECKI, W Über den Einfluss der Hereditat auf die Bildung des Magengeschwurs, Wien Klin Wchnschr, 1910, xxiii, 661-664
- 5 PLAUT, A Über Saurebefunde und Altersverhältnisse bei Ulcus ventriculi, Arch f Verdauungskr, 1913, xix, 23-41
- 6 VERBRUYCKE, J R, JR Cases of hereditary tendency to gastric ulcer, Interstate Med Jr, 1915, xxii, 844-845
- 7 PLITEK, V Über das familiäre Auftreten des Ulcus ventriculi, Arch f Verdauungskr, 1914, xx, 461-468
- 8 SPIEGEL, E Beiträge zur klinischen Konstitutionspathologie II Organdisposition bei Ulcus pepticum, Deutsch Arch f klin Med, 1918, cxxvi, 45-60
- 9 HURST, A F, and STEWART, M J Gastric and duodenal ulcer, 1929, Humphrey Milford, Oxford Univ Press, London
- 10 STRAUSS, H Über hereditäres und familiäres Vorkommen von Ulcus ventriculi et duodeni, Munch Med Wchnschr, 1921, lxxvii, 274-275
- 11 DAUWE, F L'heredité de l'ulcere rond de l'estomac, Arch mal de l'appar digest, 1913, vii, 375-383
- 12 MATHIEU, A, and MOUTIER, F Pathogenie de l'ulcere de l'estomac, Arch mal de l'appar digest, 1909, iii, 445-474
- 13 DRAPER, G, and TOURAINF, G A Man environment unit and peptic ulcer, Arch Int Med, 1932, xlix, 616-662
- 14 BLOOMFIELD, A L Clinical aspects of gastric secretion, ANN INT MED, 1932, vi, 307-313
- 15 HUDDY, G P B A study of the family histories of 300 patients suffering from chronic upper abdominal lesions Lancet, 1925 ii 276-278
- 16 WILKIE, D P D Duodenal ulcer in the female, cholecysto-duodenal syndrome, Lancet, 1927, ii, 1228-1231
- 17 MENASCI, R A proposito dell'esistenza d'una predisposizione familiare nelle ulcere gastro-duodenali, Morgagni, 1930, lxxii, 990-998
- 18 RUHMANN, W Ergebnisse zur Frage der Konstitution bei Ulcus pepticum, Deutsch Med Wchnschr, 1925, ii, 2032
- 19 BRITT Quoted by Menasci
- 20 ZISA, S Il fattore costituzionale nella genesi dell' ulcera peptica, ricerche antropometriche, Arch di pat e clin med, 1924, iii, 454-472
- 21 ASCHNER, B Über Konstitution und Vererbung beim Ulcus ventriculi und duodeni, Ztschr f d ges Anat, 1923, ix, 6-46
- 22 BAUER, J Disposition, 1921, 433
- 23 BAUER, J, and ASCHNER, B Konstitution und Vererbung bei Ulcus pepticum ventriculi und duodeni, Klin Wchnschr, 1922, i, 1250, 1298
- 24 WARTHIN A S Heredity of carcinoma in man, ANN INT MED, 1931, iv, 681-696
- 25 (a) PERISSE De l'ulcere de l'estomac et de certains accidents gastriques chez les hysteriques, These de Paris, 1876
- (b) GILLES DE LA TOURETTE L'ulcère rond de l'estomac dans les rapports avec l'hystérie, Semaine méd, 1899, 377

TOXICOLOGY AND ASSAY OF METHYLENE BLUE ⁺

By DAVID I MACHT, M D , F A C P , and WILTON C HARDEN, P H D ,
Baltimore, Maryland

INTRODUCTION

METHYLTHIONINE chloride, or methylene blue, is recognized by the United States Pharmacopoeia but its administration has hitherto been only by mouth. Recently, however, considerable publicity has been given its intravenous use in cases of cyanide and carbon monoxide poisoning. This therapeutic application of the dye has been the direct result of the most interesting laboratory investigations of Matilda M. Brooks ^{1, 2, 3, 4} and clinical reports of J. C. Geiger ^{5, 6}.

The value of methylene blue in the treatment of cyanide poisoning has been described by earlier writers. Thus, Sahlin ⁷ demonstrated its antidotal action in 1926, and Eddy ^{8, 9} also found that methylene blue stimulated the respiration and counteracted the poisonous effects of sodium cyanide. Hanzlik ¹⁰ also mentions experimental work on this subject. Gessell, Kreuger, Nicholson, Brassfield and Pelecovich ¹¹ also found that methylene blue, administered intravenously to dogs, furthered their recovery from sodium cyanide poisoning. Warburg and Christian ¹² studied the mechanism of this action.

In regard to the effects of methylene blue on carbon monoxide poisoning, the theory upon which Matilda Brooks proceeded in her experiments was based chiefly on the brilliant researches of Warburg, ^{13, 14} who showed that methylene blue has an action antagonistic to that of CO upon the oxygen consumption of yeast cells. Later, Warburg, Kubowitz and Christian found that the oxygen uptake of red blood cells is practically unaffected by carbon monoxide in the presence of enough methylene blue ¹⁵, and Ambrus, Banga and Szent-Gyorgyi ¹⁶ further found that methylene blue was reduced not only by yeast but also by various animal tissues to methylene white. Cook, Haldane and Mapson ¹⁷ found that oxidation of succinate to fumerate, lactate to pyruvate and fumerate to bicarbonate is little affected by CO if methylene blue be present.

Methylene blue has been utilized by biologists for studying oxidation and reduction of the most varied character. That methylene blue increases the oxidation of animals has been shown by the work of many authors, especially that of Heymans and Heymans, ¹⁸ Barron, ¹⁹ and Harrop and Barron ²⁰.

Elsner ²¹ found that methylene blue affects the respiration of plant cells. Watanabe ²² found that the respiration of various algae was stimulated by methylene blue. Sunzeri ²³ found that methylene blue, added to dog's liver,

* Received for publication July 5, 1933.

From the Chemical and Pharmacological Research Laboratories, Hynson, Westcott and Dunning, Inc., Baltimore, Maryland.

accelerates lipodieresis Wieland and Mitchell²⁴ discovered that methylene blue tended to reduce xanthine Bertho and Gluck²⁵ established the fact that methylene blue hastened the dehydrogenation of glucose under certain conditions Wolfson²⁶ found that this dye affects the production of catalase, and Roffo²⁷ used methylene blue as a hydrogen acceptor in the treatment of carcinoma The activation of fermentation of living tissue was further studied by Rosenthal²⁸ Very recently, Himwich and his co-workers^{29, 30, 31} studied the effect of methylene blue and cyanide on the respiration of the brain, testicle, liver and kidneys, and on the metabolism of rats

With regard to the pharmacology of this dye, Gregoire³² noted that methylene blue raises the temperature and profoundly affects the metabolism of rats Perfusing the dye through the legs of a dog, Bornstein and Pantke³³ found that small doses produced a primary dilatation followed by constriction of the vessels, while larger doses produced an immediate constriction, and a rise in blood pressure with stimulation of respiration after administration of the drug has been described by various authors Recently, while studying the effects of methylene blue on blood by phytopharmacologic methods, Macht found that this dye antagonizes the poisonous action of carbon monoxide hemoglobin and that it also neutralizes in vitro the toxins of certain diseases, especially that of pemphigus³⁴

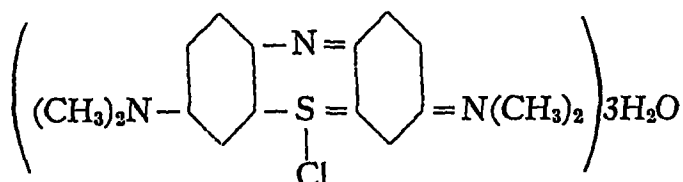
PURPOSE OF THE PRESENT WORK

The object of the present research was to secure a *reliable* and *safe* preparation of the dye for intravenous injection in clinical cases Samples of methylene blue on the market were obtained and compared as to their purity and toxicity by chemical and pharmacologic methods Methylthionine chloride is a complicated organic mercurial Now it is well known that most dyes intended for commercial and technical uses are contaminated by impurities, or diluted with such substances as dextrose, sodium chloride, sodium sulphate, etc For intravenous injection in human beings such preparations, of course, are in no wise suitable It is imperative that a chemically pure drug be obtained for such administration Furthermore, a search through the literature reveals that the potency of this drug for different animals varies greatly, and that the data gathered by a number of investigators regarding the toxicity of methylene blue for the same species of animal also show a wide divergence, which fact probably indicates variations in the composition of different samples studied by these respective workers The toxicology of methylene blue has been studied by Meyer,³⁵ Caseneuve,³⁶ Ehrlich and Leppmann,³⁷ Garfouinkel and Gautrelet,³⁸ and other writers A complete bibliography on the subject is furnished by Fuhner's chapter on methylene blue in Heffter's *Handbuch*,³⁹ and by Flury and Zernik⁴⁰ in Abderhalden's *Handbuch* The data gleaned from these are confusing and leave the investigator in much doubt as to the purity of the compounds employed, on the one hand, and their correct dosage and toxicity, on the

other A uniform and simple method of pharmacological assay is therefore much to be desired In the present work, an attempt is made to clarify this subject for practical purposes

CHEMICAL EXAMINATION

Methylene blue is a tetra-methyl-thionine chloride, having an empirical formula of $C_{16}H_{18}N_3SCl \cdot 3H_2O$ Its molecular weight is 373.4 The structural formula as given by Fuhner is



We have examined five different samples of methylene blue by chemical methods Each of these samples, marked "Methylene Blue" or "Methylthionine Chloride, U S P, Medicinal," was supposed to be a high-grade product intended for internal use These specimens were analyzed for their chlorine and nitrogen content in order to obtain an indication as to their purity The calculated theoretical percentage of chloride in methylene blue is 9.48 The calculated theoretical percentage of nitrogen in the molecule is 11.24 Table 1 shows the percentages of chlorine and nitrogen in the five samples of dye analyzed It will be noted that the chemical composition of the various samples examined differed greatly and, on analysis, only one of the samples, No. 4, which was a chemically pure product, gave figures approximating those of theoretical calculation One of the specimens contained 0.48 per cent of inorganic sulphur

TABLE I

Specimen of Methylene Blue	Chemical Analysis		Pharmacologic Test
	Per cent of Chlorine (Theoretical, 9.48%)	Per cent of Nitrogen (Theoretical, 11.24%)	Lethal Dose in Milligrams per Kilo Weight of Cats
No. 1	9.18 per cent	10.54 per cent	100 milligrams
No. 2	8.60 per cent	10.30 per cent	51 milligrams
No. 3	19.68 per cent	6.83 per cent	210 milligrams
No. 4	9.38 per cent	11.00 per cent	41 milligrams
No. 4	9.38 per cent	11.00 per cent	54 milligrams (after autoclaving)
No. 5	8.00 per cent	10.85 per cent	75 milligrams

PHARMACOLOGIC EXAMINATION

A consideration of many discrepancies between the reports of various investigators cited in older literature on the subject made it desirable to test

the potency of different specimens of methylene blue pharmacologically. Toxicologic experiments were made with intraperitoneal injections in mice, rats and guinea pigs, with subcutaneous injections in guinea pigs and with intravenous injections in rabbits and cats. After considerable preliminary investigation, it was found that the most valuable information on the subject could be deduced from carefully planned experiments on cats.

The method of procedure was as follows. Full-grown cats were anesthetized and kept constantly under ether by inserting a tracheal cannula connected with a respiratory bottle. Blood pressure tracings from the carotid artery were made on a slowly revolving kymograph, and tracings of the respiratory movements were obtained by a special method described by one of the authors elsewhere.²¹ A cannula was inserted into the femoral vein. A 0.5 per cent solution of methylene blue in physiological sodium chloride was then injected into the femoral vein of the cat at regular intervals from a burette. The effect of the injection of one c.c. of the solution a minute upon the blood pressure and respiration and other functions of the body was noted. It was found that an injection of one c.c. of 0.5 per cent of methylene blue promptly produced a rise in blood pressure, which returned to normal, however, at the end of a minute. Subsequent injections at one-minute intervals produced the same effect, namely, a sharp rise in the blood pressure with return to normal. When the injections were increased in number, however, the rises gradually became less marked and the blood pressure finally dropped suddenly to a dead level. Simultaneously with the rise in blood pressure produced by injections of the dye, a slight stimulation of both the frequency and amplitude of the respiration was noted. When the blood pressure reached the lethal stage, the respiration continued and indeed was stimulated for a minute or two after cessation of the heart-beat. Injections of methylene blue were also found to produce a marked hyperpyrexia or rise of several degrees in the animal's temperature, which could be detected merely by touching its body with the naked hand or be measured with a thermometer. After injection of large doses of the methylene blue, the blood turned chocolate in color and gave evidence of the formation of methemoglobin.

Experiments like those described above were repeatedly made with different samples of methylene blue. The results obtained are exhibited in the foregoing table in which, for the sake of completeness, are also shown the findings obtained on chemical analysis of the different specimens. It was found that the minimal lethal dose of the chemically pure sample of methylene blue, No. 4, was 41 mg. per kilo weight for cats. The minimal lethal doses of the other four samples examined were all greater than that of the chemically pure substance, although all the specimens had been labelled, "Methylene Blue, U. S. P.—Medicinal." In figure 1 is reproduced the kymographic record of one of the experiments. Here are shown the tracings made of the blood pressure, respiratory movements, and also the time on a slowly turning drum.

THE METHOD OF STERILIZING METHYLENE BLUE SOLUTIONS

Earlier investigators have found that methylene blue itself is antiseptic to a certain degree. We have found that the simplest and safest way of sterilizing such solutions was to boil them for a few minutes over the open flame or to heat them on the waterbath from 10 to 15 minutes. We experimented on the effects of sterilizing the methylene blue solutions in an autoclave under pressure. However, it was found that such solutions underwent

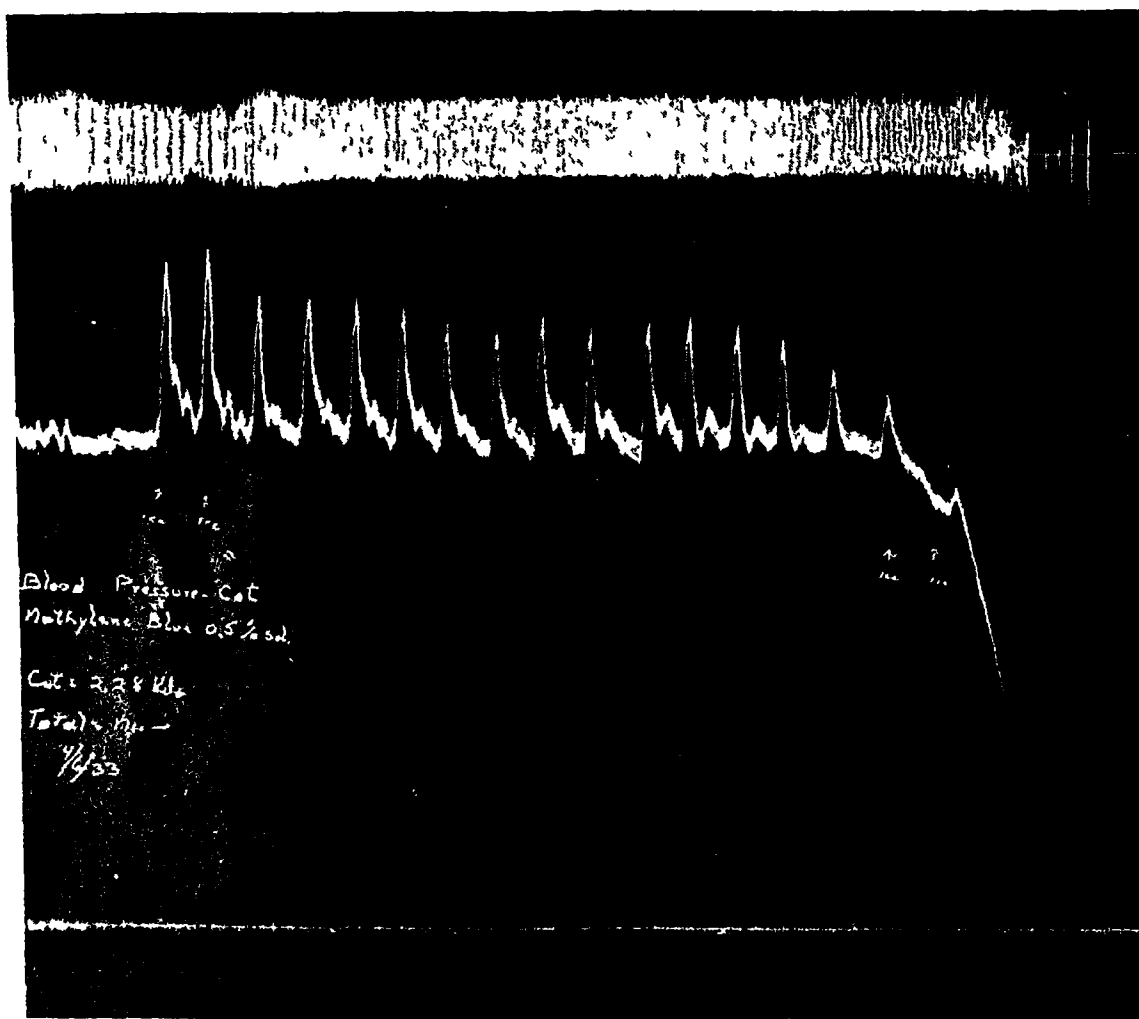


FIG 1 Intravenous injection of chemically pure methylthionine chloride. Effect on blood pressure and respiration

considerable decomposition. The dye became demethylated to some extent and yielded methyl alcohol and another dye known as Lauth's violet. A pharmacologic test with such partially decomposed solutions of methylene blue revealed that they were less toxic than the original solution. Thus it will be seen that the average lethal dose for cats of a specimen of methylene blue sterilized in the autoclave was 54 mg per kilo.

The keeping qualities of solutions of methylene blue are somewhat in

question but we have had no serious difficulties in this respect. After such solutions had been sterilized on the waterbath and boiled, practically no precipitate was noted. However, it has been suggested that solutions of methylene blue, made up with sodium sulphate, may keep better after several weeks have expired. To this procedure there can be no objection because, when injected intravenously, the sodium sulphate in such solutions would tend to lower the toxicity of the dye.

DISCUSSION

The results of pharmacologic experiments not only on cats but also on other animals impress us with the fact that methylene blue, especially when administered intravenously, is by no means an innocuous substance, and the more chemically pure the dye is, the more potent it is pharmacologically. It is furthermore interesting to note that samples of methylthionine chloride on the market, even though labeled, "U S P, Medicinal," show marked variations in chemical composition and toxicity. It is therefore very desirable in all pharmacologic and therapeutic experiments with this drug to use a preparation which is chemically pure and which has been assayed in regard to its potency. Without passing judgment on the value of methylene blue as a therapeutic agent in the various conditions in which it has already been advocated and used, it is our opinion that all the results to be expected from its use could be obtained equally well and with greater safety with smaller doses of the dye than those which have been recommended up to the present time in clinical papers on the subject. The recently published studies of one of the writers concerning the effects on living plants of very dilute solutions of methylthionine chloride, and the detoxification thereby of a number of toxins in the blood, corroborate this view. We should not recommend the administration of 50 c c of a 1 per cent solution of methylene blue as a single dose for intravenous injection in human beings but rather doses of from 10 to 20 c c of a 0.5 per cent solution, which could be repeated if desired.

SUMMARY

1 Chemical and pharmacologic examination of various samples of "medicinal" methylene blue on the market reveals that they differ greatly in their purity.

2 A method of assay of methylthionine chloride for intravenous administration has been described.

3 The lethal dose of chemically pure methylthionine chloride administered intravenously to cats is about 40 mg per kilo weight.

4 It is suggested that whenever the therapeutic effects produced by methylthionine chloride are desired, the results may be obtained more safely by administering smaller doses of the dye than those which have been recently recommended for intravenous injection.

REFERENCES

- 1 BROOKS, M M Effect of methylene blue on CN and CO poisoning (preliminary report), *Proc Soc Exper Biol and Med*, 1932, xxix, 1228-1229
- 2 BROOKS, M M Effect of methylene blue on HCN and CO poisoning, *Am Jr Physiol*, 1932, cii, 145-147
- 3 BROOKS, M M Methylene blue as antidote to CO poisoning (preliminary report), *Proc Soc Exper Biol and Med*, 1933, xxx, 493-494
- 4 BROOKS, M M Methylene blue as antidote to CO poisoning, *Am Jr Physiol*, 1933, civ, 139-141
- 5 GEIGER, J C Cyanide poisoning in San Francisco, *Jr Am Med Assoc*, 1932, xcix, 1944-1945
- 6 GEIGER, J C Methylene blue solutions in treatment of carbon monoxide poisoning, *Jr Am Med Assoc*, 1933, c, 1103-1104
- 7 SAHLIN, B Antagonism between methylene blue and potassium cyanide, *Arch f Physiol*, 1926, xlvii, 284
- 8 EDDY, N B Antagonism between methylene blue and sodium cyanide, *Jr Pharm and Exper Therap*, 1930, xxxix, 271
- 9 EDDY, N B Regulation of respiration, antagonism between methylene blue and sodium cyanide, *Jr Pharm and Exper Therap*, 1931, xli, 449-464
- 10 HANZLIK, P J Methylene blue as antidote for cyanide poisoning, *Jr Am Med Assoc*, 1933, c, 357
- 11 GESSELL, R, and others Comparison of response of anesthetized dog to intravenous administration of sodium cyanide during uniform artificial ventilation and during normally controlled ventilation with additional observations on effects of methylene blue, *Am Jr Physiol*, 1932, c, 227-240
- 12 WARBURG, O, and CHRISTIAN, W Über ein neues Oxydationsferment und sein Absorptionsspektrum, *Biochem Ztschr*, 1932, ccliv, 438
- 13 WARBURG, O Über die Grundlagen der Wielandschen Atmungstheorie, *Biochem Ztschr*, 1923, cxlii, 518-523
- 14 WARBURG, O Über die Wirkung des Kohlenoxyds auf den stoffwechsel der Hefe, *Biochem Ztschr*, 1926, clxxvii, 471-486
- 15 WARBURG, O, KUBOWITZ, F, and CHRISTIAN, W Über die katalytische Wirkung von Methylenblau in lebenden Zellen, *Biochem Ztschr*, 1930, ccxxvii, 245-271
- 16 AMBRUS, P, BANGA, I, and SZENT-GYORGYI, A Beiträge zur Methodik der Messung des Sauerstoffverbrauchs, des Respirationsquotienten und der Methylenblaureduktion der Gewebe und der Hefe, *Biochem Ztschr*, 1931, ccxi, 473-477
- 17 COOK, R P, HALDANE, J B S, and MAPSON, L W Relationship between respiratory catalysts of *B coli*, *Biochem Jr*, 1931, xxv, 534-550
- 18 HEYMAN, J F, and HEYMAN, C Hyperthermia and increase of the respiratory volume and of the elimination of carbon dioxide produced by methylene blue, *Arch Internat Pharmacodynamie*, 1922, xxvi, 443
- 19 BARRON, E S G Studies on blood cell metabolism, effect of methylene blue on oxygen consumption of eggs of sea urchin and starfish, mechanism of action of methylene blue on living cells, *Jr Biol Chem*, 1929, lxxxii, 445-459
- 20 HARROP, G A, and BARRON, E L G Studies on blood metabolism II The effect of methylene blue and other dyes upon the glycolysis and lactic acid formation of mammalian and avian erythrocytes, *Jr Exper Med*, 1928, xlviii, 207
- 21 EISNER, W Action of methylene blue on living plant cells, *Ztschr f Wissensch Mikr*, 1932, xlix, 28
- 22 WATANABE, A Physiology of the metabolism of algae I Influence of potassium cyanide and methylene blue on the respiration of some green algae, *Acta phytochim*, 1932 vi, 315
- 23 SCHAFER, G The action of certain photodynamic substances on lipodieresis, *Boll d Soc ital di biol sper*, 1932 vii, 740

- 24 WIELAND, D, and MITCHELL, W Mechanism of oxidation processes XXIX Dehydrogenating enzymes of milk, Liebig's Annalen, 1932, cdxci, 156
- 25 BERTHO, A, and GLUCK, H Respiratory processes of lactic acid bacteria, Liebig's Annalen, 1932, cdxci, 159
- 26 WOLFSON, I A The influence of dyes on the formation of catalase in certain bacteria, Arch sci biol (U S S R), 1931, xxi, 161
- 27 ROFFO, A H Oxydo-Reduktion in der Krebsbehandlung, Ztschr f Krebsforsch, 1932, xxxvii, 1-9
- 28 ROSENTHAL, O Versuche über die Aktivierung der anaeroben Gärung von Lebergewebe durch Brenztraubensäure, Acetaldehyd und Methylenblau, Biochem Ztschr, 1932, ccxiv, 133-156
- 29 HIMWICH, H E, FAZIKAS, J F, and HURLBURT, M H Effect of methylene blue and cyanide on respiration of cerebral cortex, testicle, liver and kidney, Proc Soc Exper Biol and Med, 1933, xxx, 904-906
- 30 HIMWICH, H E, and GOLDFARB, W Effects of methylene blue on respiratory metabolism of rat, Proc Soc Exper Biol and Med, 1933, xxx, 906-907
- 31 HIMWICH, H E, and others Effect of methylene blue on R Q of brain in situ, Proc Soc Exper Biol and Med, 1933, xxx, 907-908
- 32 GREGOIRE, P Action of methylene blue on body temperature and metabolism, Jr Exper Med, 1931, liv, 827-845
- 33 BORNSTEIN, A, and PANTKE, R Die Gefasswirkung des Methylenblaus, Arch f exper Path u Pharm, 1931, clxi, 229-232
- 34 MACHT, D I Effect of methylthionine chloride on phytotoxic reaction of normal and pathological blood, Proc Nat Acad Sci, 1933, xix, 486-491
- 35 MEYER, S Die subcutane Methylenblauinjection, ein Mittel zur Darstellung der Elemente des Centralnervensystems von Säugethieren, Arch f mikr Anat, 1895, xlv, 282-290
- 36 CASENEUVE La coloration des vins, Paris, 1886, 89
- 37 EHRLICH, P, and LEPPMANN, A Über schmerzstillende Wirkung des Methylenblau, Deutsch med Wchnschr, 1890, xvi, 493
- 38 GARFUNKEL, I G, and GAUTRELET, J Contribution à l'étude de l'action des matieres colorantes sur la coeur et la pression, Compt rend Acad d sci, 1913, clvii, 1464-1466
- 39 FUHNER Handbuch der experimentellen Pharmakologie, A Heffter, Berlin, 1923, i, 1268
- 40 FLURY, and ZERNIK Handbuch der biologischen Arbeitsmethoden, Emil Abderhalden, 1928, Abt IV, Teil 7, Heft 7, Lieferung 251, 1366
- 41 MACHT, D I A simple method of studying respiratory pharmacodynamics, Jr Am Pharmaceut Assoc, 1930, xix, 7

CONSERVATISM, THE KEYNOTE IN THE TREATMENT OF TUBERCULOSIS *

By C H COCKE, M D , F A C P , *Asheville, North Carolina*

WHEN a diagnosis of pulmonary tuberculosis has been made, the planning out of a mode of treatment entails considerably more than the immediate relief of the presenting symptoms. To attempt a finally definitive outline at once, and particularly to essay a prognosis until more is known of the case, is hazardous and will frequently bring disappointment. Hasty judgment in all medical matters is to be deplored, in tuberculosis it is to be condemned in no uncertain terms.

To begin with, it must be insisted that the tuberculous patient presents a problem that is quite different from that found in most chronic diseases. Any plan of treatment that may be expected to offer hope of arrestment, if not full recovery, must be predicated upon the assumption of the patient's willingness and ability to see it through. In any such plan, time is of the essence, time and more time, and most efforts to shorten unduly this element end in disappointment and frequently in disaster. Other variable factors which make the treatment of the tuberculous an engrossing and ever changing challenge are the patient's age, his social and economic background, his disposition, temperament, and character, his patience and courage and willingness for sacrifice of time and family, his intellectual background and resources for harmless interests and entertainments, his habits of life and habits of thought, his spirit of cooperation or rebellion, and particularly the imponderable factors of the reaction of the individual host to the given invader. While it is fairly well known what happens when the tubercle bacillus invades the human organism, whether for the first time or for subsequent attack, this knowledge does not extend to any degree of certainty as to what will happen in any given case of *clinical tuberculosis*. The mere matter of the geographical location of the tuberculous lesion, or the chance occurrence of a complication, may make what started out as an apparently harmless or mild disease suddenly become an extremely severe and disabling one¹. The addition of an acute respiratory infection leaves one case that was only mildly active sadly reactivated, and apparently a similar case, with like accident, goes on to an uninterrupted arrest, as though nothing unusual had happened. A small hemorrhage occurs, and a previously sluggish lesion apparently makes more rapid and satisfactory progress, another hemorrhage may be followed by miliary spread of the disease. One could go on at length with the recital of the uncertainties of the progress of any given case of tuberculosis, as compared with any other given case of *apparently similar* extent and kind. In the end, one must conclude that each

* Presented before the General Session of the American College of Physicians, 17th Annual Session, Montreal, Canada, February 8, 1933

individual case of tuberculosis is in some measure *sui generis*, and, for successful treatment, must be studied and managed as a separate and individual problem, with only certain fundamental factors in the treatment known. Tuberculosis, as a disease, cannot often be successfully treated, *patients* with tuberculosis can and are treated successfully by the thousands. The art as well as the science of medicine must be applied, mere science in this instance is rarely enough.

In no other disease is the problem of the assay of the results of treatment more difficult than in tuberculosis. As each case is, as I have stated, a law unto itself, the difficulty of obtaining control observations is well nigh insuperable, as there is no sure way of selecting comparable controls. So many cases get well with only rest treatment, and that sometimes in the sketchiest of forms, that one should pause before attributing to any specific added form of treatment the success finally achieved. Hence the futility of attempting, for instance, to evaluate the effect of climate and rest as compared with that of compression and surgical procedures. Such comparisons do not fall within the purpose of this paper. Its purpose is rather to attempt to demonstrate the truth of a principle which I feel is fundamental in the treatment of any given case of tuberculosis, namely that of all the measures that up to the present time have been given a trial, *rest is the only specific*, and that conservatism in the management of the case is generally rewarded.

Some years ago Dr. Robert T. Morris pointed out that surgery had gone through four evolutionary eras: the Homeric period of its earliest efforts, the roughly Anatomic period, the Pathologic period (based on Virchowian cellular pathology), and the present day Physiologic era, in which the surgeon's dual purpose is the eradication of pathologic processes and the restoration of physiologic function. Quite similarly the treatment of tuberculosis may be said to have passed through certain well defined phases.

Perhaps the first successful effort at treatment of tuberculosis was made by Brehmer and Dettweiler. Theirs, however, was only a partial success, for Brehmer to the end maintained that *exercise* was the curative factor, while Dettweiler found the sovereign factor in fresh air, both failed to realize that the rest they gave their patients *incidentally* was in all probability the chief factor in their success. Of the Climatic era, at least in this country, little need here be said. It is sufficient to observe that even if at present no man claims that climate alone will cure tuberculosis, he would be more than rash who claimed that there were not certain climates inherently beneficial to the tuberculous. As Lawrason Brown insists, almost any change helps the tuberculous patient, and, if that change can be to a locality or climate where the pursuit of his cure is made more easy and certain, so much the better for the patient. My own position in the matter can be summed up in the aphorism, *it is infinitely more important what the tuberculous patient does than where he does it*, or as Osler phrased it, "care without climate is better than climate without care."

The Tuberculin era followed, and in its wake came a series of biologic

and chemotherapeutic efforts that have all fallen short of success Today in treatment tuberculin has, in my opinion, an extremely limited application, in diagnosis, it is an invaluable measure Of the chemicals, gold and sodium thiosulphate, Sanocrysin has perhaps met with more success than any other, and yet its use is quite limited, and it is a hazardous drug improperly applied

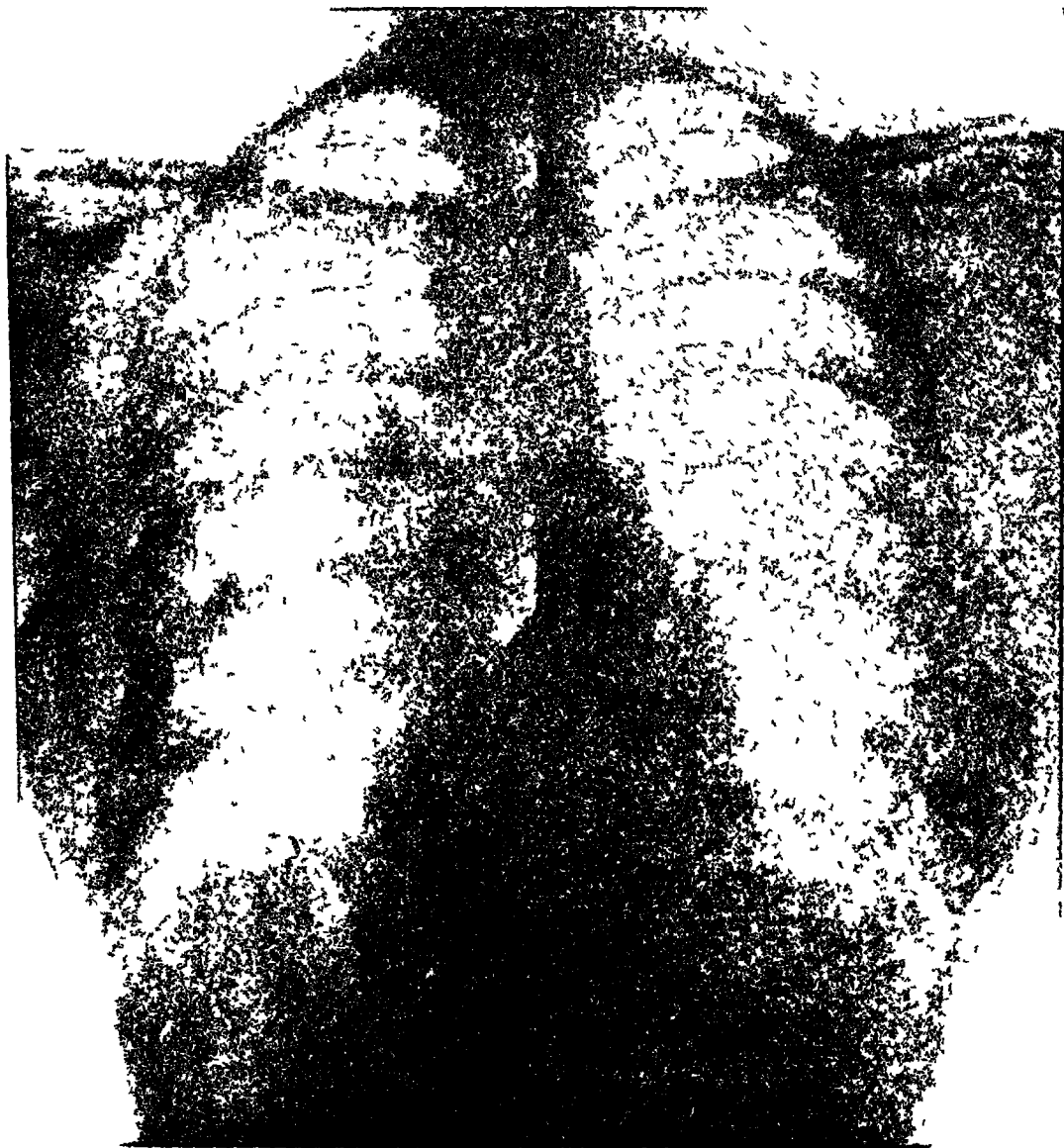


FIG 1 Case I T M, female, age 23 July 11, 1928 Marked, right-sided infiltration, cavity second interspace, left lower lobe infiltration

The Sanatorium and Rest era (for the latter became possible because of the former) gave us our first real conception of the true nature of the healing factor in the cure Recently Pratt of Boston has well traced the evolution of the rest cure in tuberculosis, and I can add nothing to his interesting paper It is scarcely necessary to expand upon the value of rest, it remains, as Krause has well insisted, *the only proved specific* in the treatment of the disease

The Compression era was started by a growing knowledge of the value of Forlanini's work in pneumothorax. Of external appliances for attempted immobilization, shot bags, pneumatic jackets, postural rest, etc., it need only be said that they all have as their chief function an effort to put the diseased lung at rest. The same statement is true likewise of the various surgical



FIG 2 Case I T M June 14, 1930 Complete clearing by resolution of practically all pathology

procedures now daily practiced wherever tuberculosis is intelligently treated, of internal pneumolysis, which allows the collapse of cavities held open by adhesions, of apicolysis, of paraffin packs, of phrenic crushings or exairesis, of intercostal and other neurectomies, of thoracoplasties, et id al. All such procedures attempt to obtain as much immobilization of the diseased lung

as the operation can accomplish and the patient's lesions will permit. We are in an era of phthisiotherapy by surgery, but in spite of the popular acclaim of these surgical measures it is well for us to pause and consider before we decide to place the treatment of tuberculosis in the domain of the surgeon.



FIG 3 Case II C W M, male, age 24. Fairly acute fulminant history of six weeks, October 2, 1926. Complete left-sided tuberculous involvement, cavity in second interspace, pneumonic consolidation midfield, slight extension to right upper.

In any discussion of compression therapy it should be recognized as a fundamental fact that artificial pneumothorax, which was the first successful compression method developed, when technically possible, is still the most successful and has the widest usefulness. In my opinion it is the one single, most brilliant advance in the treatment of tuberculosis in the past 25 years. It has been, and should be, considered entirely a medical practice as distinct from a surgical procedure, though obviously it should always be done with

the best surgical aseptic technic With advancing knowledge and accumulating experience, artificial pneumothorax has today a much wider field of usefulness and application than was thought possible in earlier days when its use was restricted to cases showing almost absolute freedom from disease of the contralateral lung Experience daily shows that fairly widespread



FIG 4 *Case II* C W M October 2, 1929 Complete disappearance of cavity Slight fibrosis in area of former consolidation

lesions in the opposite lung undergo marked absorption and healing, when the more badly diseased lung has been compressed and the burden of its toxins removed Laryngeal complications, when amenable to cauterization or other competent treatments, no longer bar us as formerly from its use This is not the place to attempt a recital of the indications for pneumothorax therapy and the choice of suitable subjects, but it does seem proper to state

that it is the almost universal tendency among the phthisiologists of today to employ artificial pneumothorax earlier and earlier in the disease. The purpose is threefold—to stop the destructive effect of the lesion and arrest its spread, to avoid the danger of a possible later inability to use the method because of pleural symphysis, and lastly to shorten the cure. This is an essentially conservative position to take on this question though I admit that



FIG 5 *Case III* Mrs B M H, age 57 June 19, 1926 Complete right-sided involvement, fibrocavernous, definite cavity in upper lobe, suggestive one in lower

as recently as 10 or possibly 15 years ago it might have been considered truly radical.

In taking up now the subject of surgical compressions it is not my object to attempt disparagement or criticism, but rather to present a plea for a proper appreciation of the value of these procedures and particularly for calm and critical judgment as to the proper time for using surgical aid. There is

undoubtedly a tendency among many to resort to surgery earlier and earlier in the disease, until I fear the danger point has been reached of assuming that surgery is a *substitute* for conservative treatment. A denial of this is my major thesis. I cannot offhand agree to the recently expressed surgical opinion that at least 75 per cent of the cases of pulmonary tuberculosis with

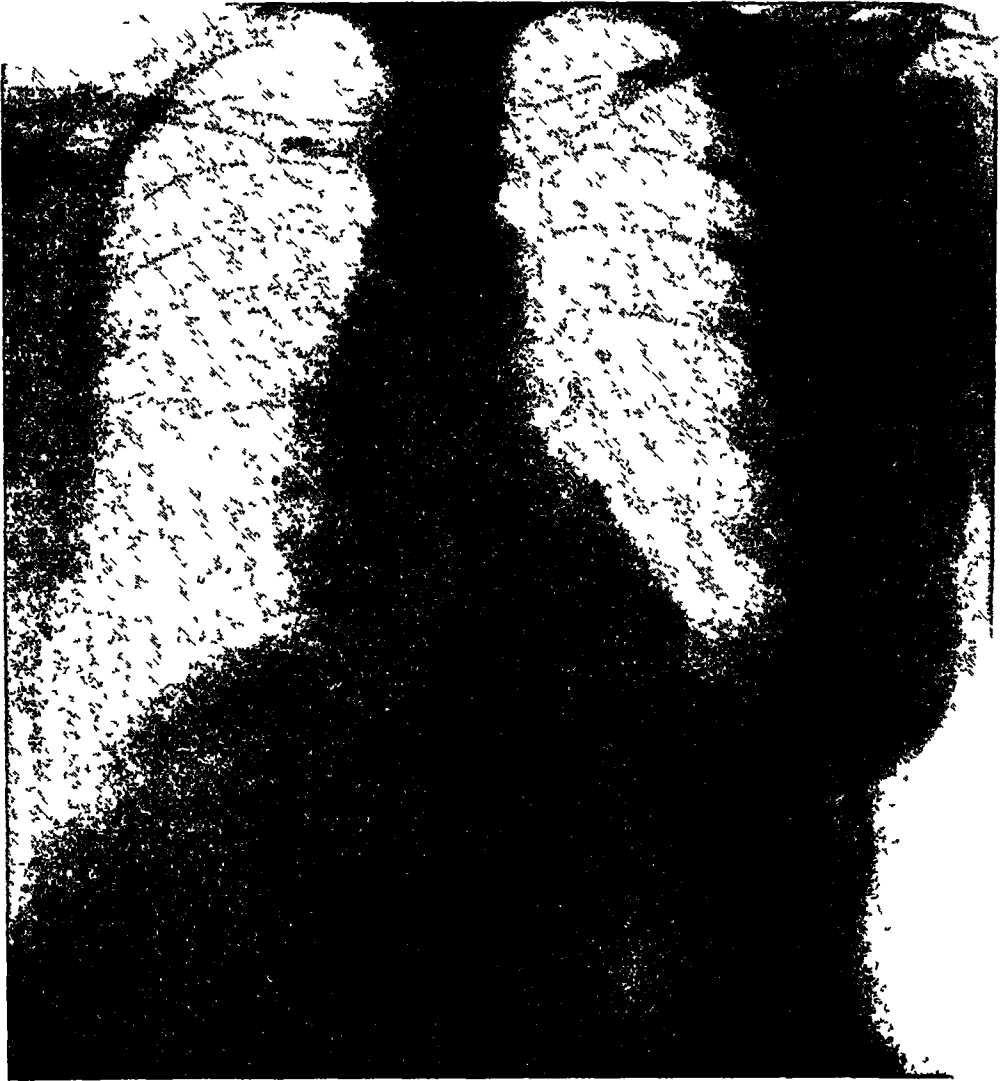


FIG 6 Case III Mrs B M H September 20, 1927 Complete clearing of all pathology save slight fibrous band

cavities should undergo some form of collapse therapy as early in the course of the disease as possible, for the very apparent reason that I know of no possible way of judging at the outset of treatment which case is to be the lucky one in four that will not require compression, nor have I heard of the proper rule for such discovery being given by our surgical colleagues. No one can presume to state categorically how extensive a tuberculous lesion can and will

be resolved or fibrosed and thus healed With the patient under conditions of ideal basal bed rest, under constant supervision, and radiographic control, I maintain that it is much better to wait and see what happens, rather than hastily to undertake surgical measures which may be needless This period of waiting does not have to be long, perhaps a month's observation may con-

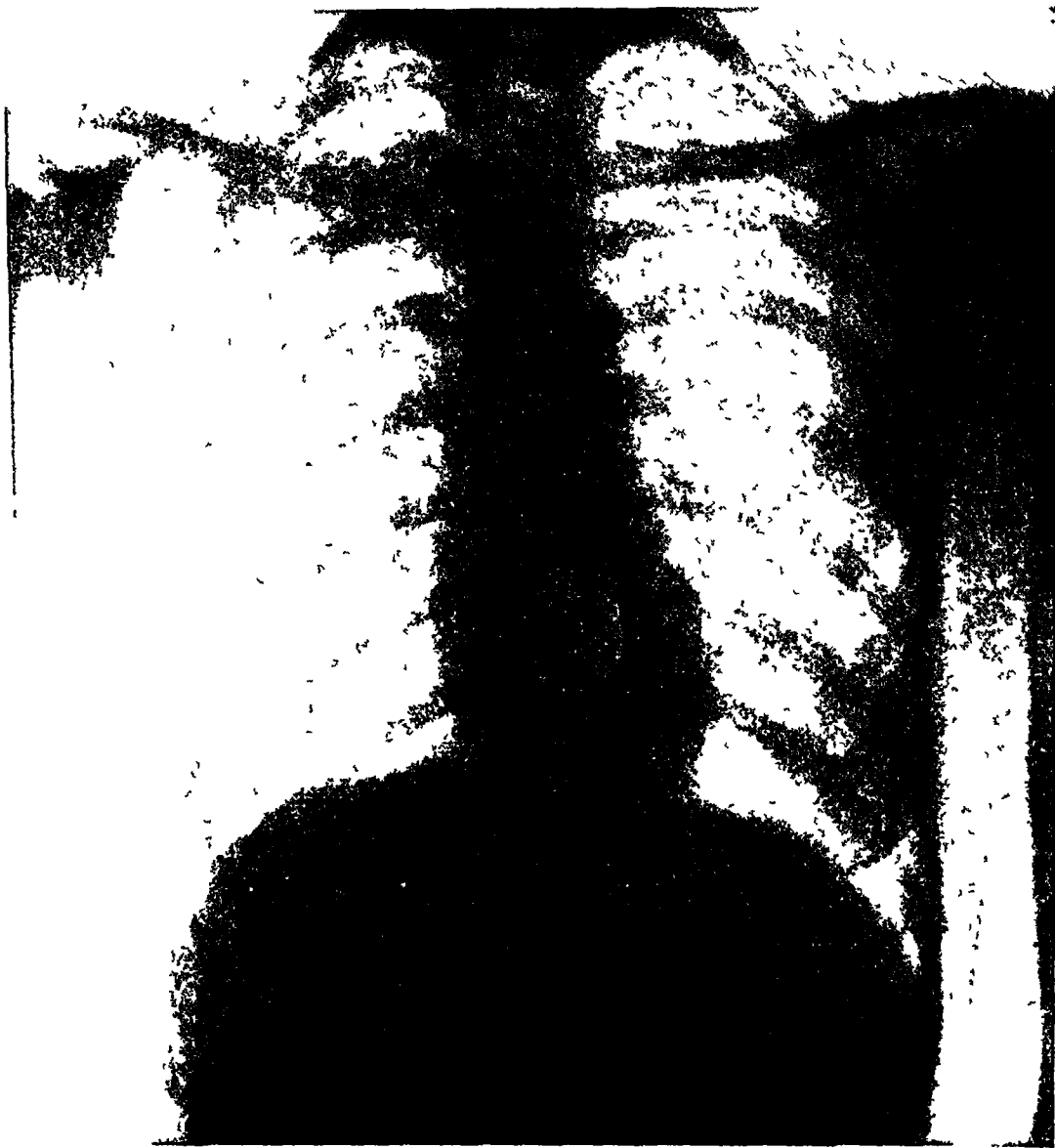


FIG. 7 *Case IV* Mrs I P B, age 26, weight 93 pounds May 19, 1926 Tuberculous infiltration and cavitation right upper lobe Well marked wall to cavity

vince one of the satisfactory turn of the case, or on the other hand of the inadvisability of further delay in resorting to some form of compression More likely it will prove best to extend this period of careful waiting to from three to six months, at the end of which time decision as to the best course to follow is made with greater surety Naturally, this program is predicated upon control of the case immediately after the diagnosis is made, because

it is quite obvious that if any great amount of time has elapsed before the patient comes under treatment there must be some modification of the above outline. Is this delay justified? In my experience it is not only justified, it has proved its value. In tuberculosis we are dealing with a problem that involves not only the patient's present but his entire future existence and activities, and it is important that the method of treatment selected

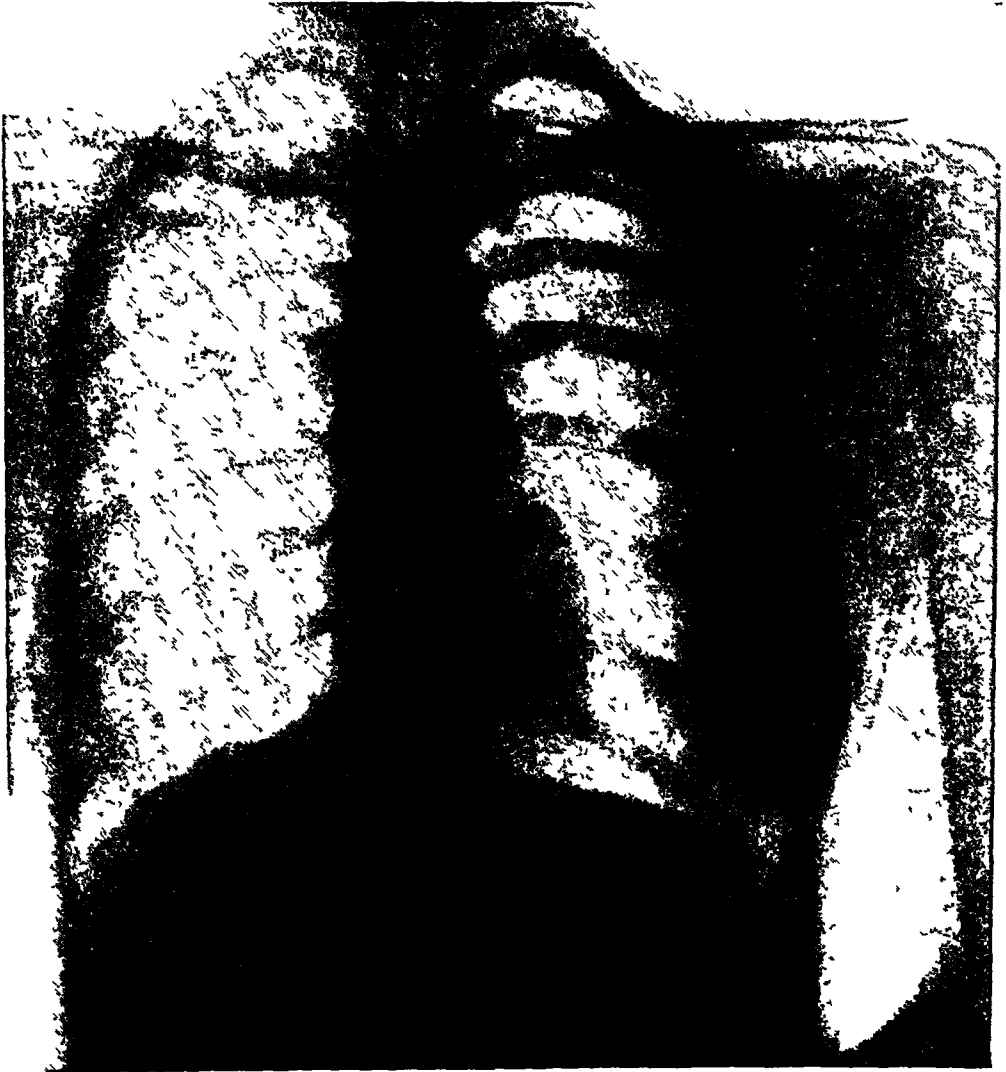


FIG 8 Case IV Mrs I P B June 10, 1927 Cavity still definitely seen

should not only give him the best help in arresting his disease but should also be the least likely to leave him with an aftermath of crippling handicaps.

A really fundamental objection to surgery in the beginning of treatment is that it is apt to give the patient an exaggerated idea of the efficacy of the surgical procedure and to diminish his appreciation of the value of the proper sort of rest and care, such as is necessary for a good many months after the

operation Surgery does not cure tuberculosis At best it puts the diseased lung at rest, and attempts a mechanical closure of cavities which nature has failed to obliterate Such being the case, no matter how brilliant the mechanical result of the surgical procedure, if the lesions are to heal much time must be given by the patient to the proper régime The rapid subsidence



FIG. 9 Case IV Mrs I P B October 24, 1929 Weight 133 pounds Complete disappearance of cavity with absorption of most of its wall

of symptoms gives the untrained patient a false sense of security that leads him inevitably into dangerous overactivities, and as a consequence he may lose the real benefits he should have derived from the operation

Throughout this discussion, I am speaking entirely from the standpoint of an internist dealing with a referred clientele of tuberculous patients of various origins, and my remarks are not in any sense to be construed as an

effort at solving the question of the best socio-economic approach to the problem of tuberculosis therapy. I can readily appreciate the zeal and enthusiasm for attempted shortcuts in therapy on the part of those dealing with large numbers of patients unable for economic or other reasons to follow the program I advocate. I am speaking of what I conceive to be the best method of approach in handling the private tuberculous patient who comes under my care.

In favor of phrenic section as a mode of compression therapy it is urged that the operation is a simple one, whether a temporary crushing is done, a section, or an exaeresis, that it rarely has serious consequences or complications, and that while it formerly had as its main field of endeavor the closures of basal cavities, its benefits are now known to extend to upper lobe cavities and also to soft lesions not yet excavated. I am not disposed to attempt to refute these statements, but when it is claimed further that it should be used in earlier and still earlier lesions, as it is in these that it demonstrates its greatest benefits, I feel that it must be pointed out that it is precisely in these same early cases that careful bed rest and supervision achieve their most brilliant results! The theory of the above argument is well enough, unfortunately in actual practice the results do not justify the glowing claims of some enthusiastic neurectomists. Even in theoretically ideal cases, I have seen the effect of phrenic section exactly nil, and such an outcome is always a serious discouragement to the patient. I believe it is always a mistake to undertake any form of compression therapy (and this is doubly true with respect to pneumothorax) with the patient convinced that in the special procedure lies his salvation. He should be carefully told what to expect, both in the matter of help and in that of possible failure, else his morale may be upset in a way that may have serious consequences. Of phrenicectomy as an aid in pneumothorax, or perhaps as an antecedent of thoracoplasty, I can speak with more enthusiasm. In the release of the so-called suspended cavity, as well as to fortify an expanding lung, where pneumothorax is to be abandoned, voluntarily or necessarily, I believe it has one of its major indications.

The question of thoracoplasty at once brings up a matter that has been often emphasized, but cannot be stressed too greatly. I refer to the necessity for thorough teamwork between a capable internist and a well trained thoracic surgeon. Competency in general and abdominal surgery by no means predicates adequate equipment to do first-class thoracic surgery. Even with the best of training, moreover, the chest team will arrive at the wisest solution of the surgical problem in any given case only through joint study and the closest of cooperation. In this special field, as I insisted earlier, the needs of each patient are highly individualized. The choice of the proper operation, the optimum time therefor, the after care, all require the most thorough collaborative study. Though in the best clinics, the immediate operative mortality rate has been lowered below 5 per cent, thoracoplasty is necessarily such a major procedure that it must not be resorted to

in cases in which there is a question of the cardiovascular system's ability to meet the stress and strain it entails, nor should it be undertaken until less hazardous forms of compression (such as pneumothorax) have failed. Again I would emphasize that the most brilliant surgical procedure does not cure tuberculosis, it merely helps mechanically to close cavities which would

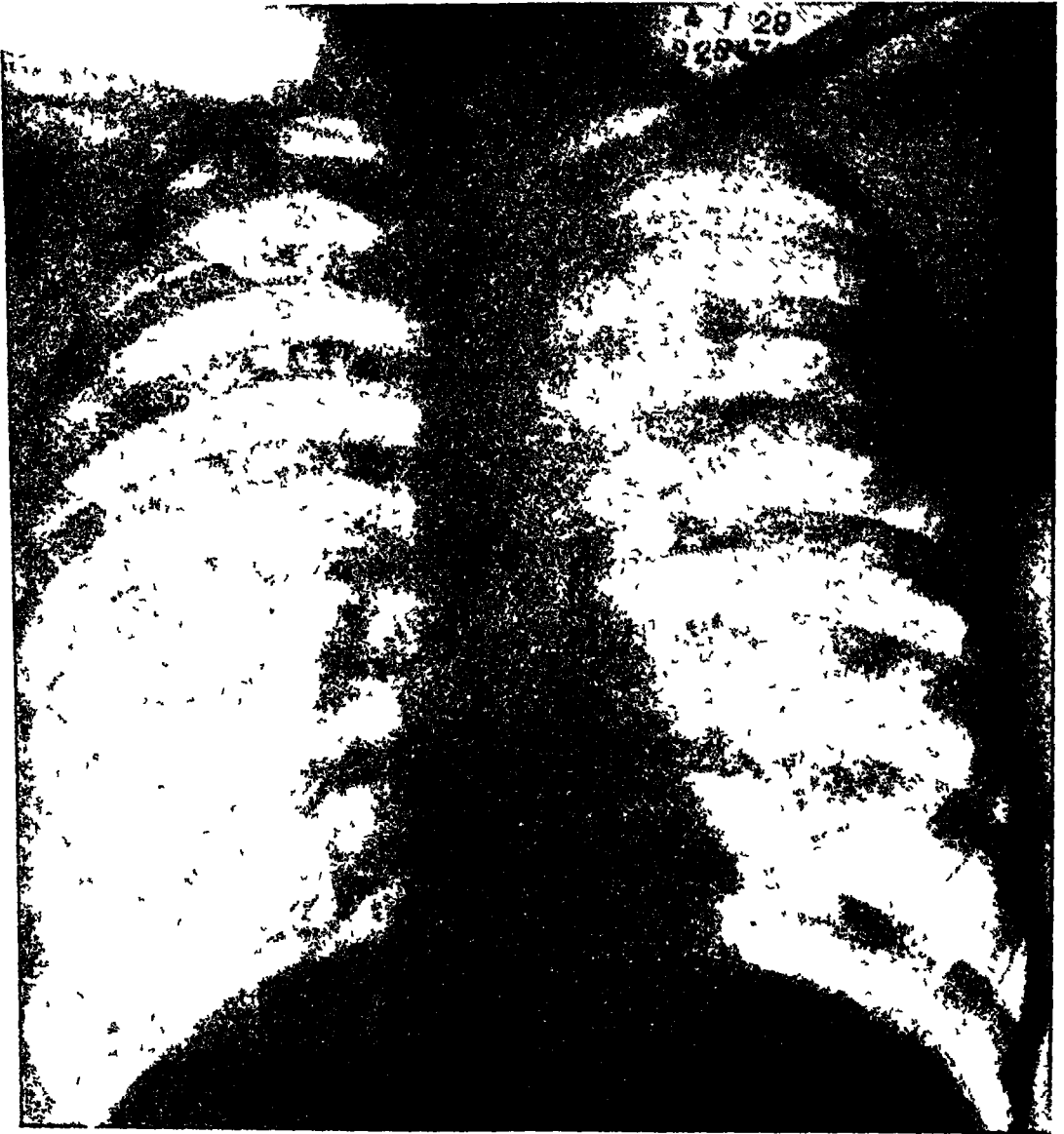


FIG. 10 Case V Dr H. E. W., male, age 31 April 1, 1929 Left upper lobe cavity, with infiltration Slight right spread

otherwise remain open and to give to the diseased lung that rest which is essential for healing. My excuse for this reiteration is the necessity for impressing upon the patient that the tuberculous lesion is there just as it was before the operation, and that time alone can cure him. The operation is *not a substitute for the healing process but an aid thereto*. In properly selected cases, operated upon at the proper time by a competent thoracic

surgeon, we may confidently look for results not achievable by conservative measures alone, but time and careful observation are essential in the choice of patients, the time of operation and its kind, all matters for individual decision upon the merits of the given case

What may one expect of this expectant and conservative approach to the problem? By conservatism, I mean the intensive application of bed-

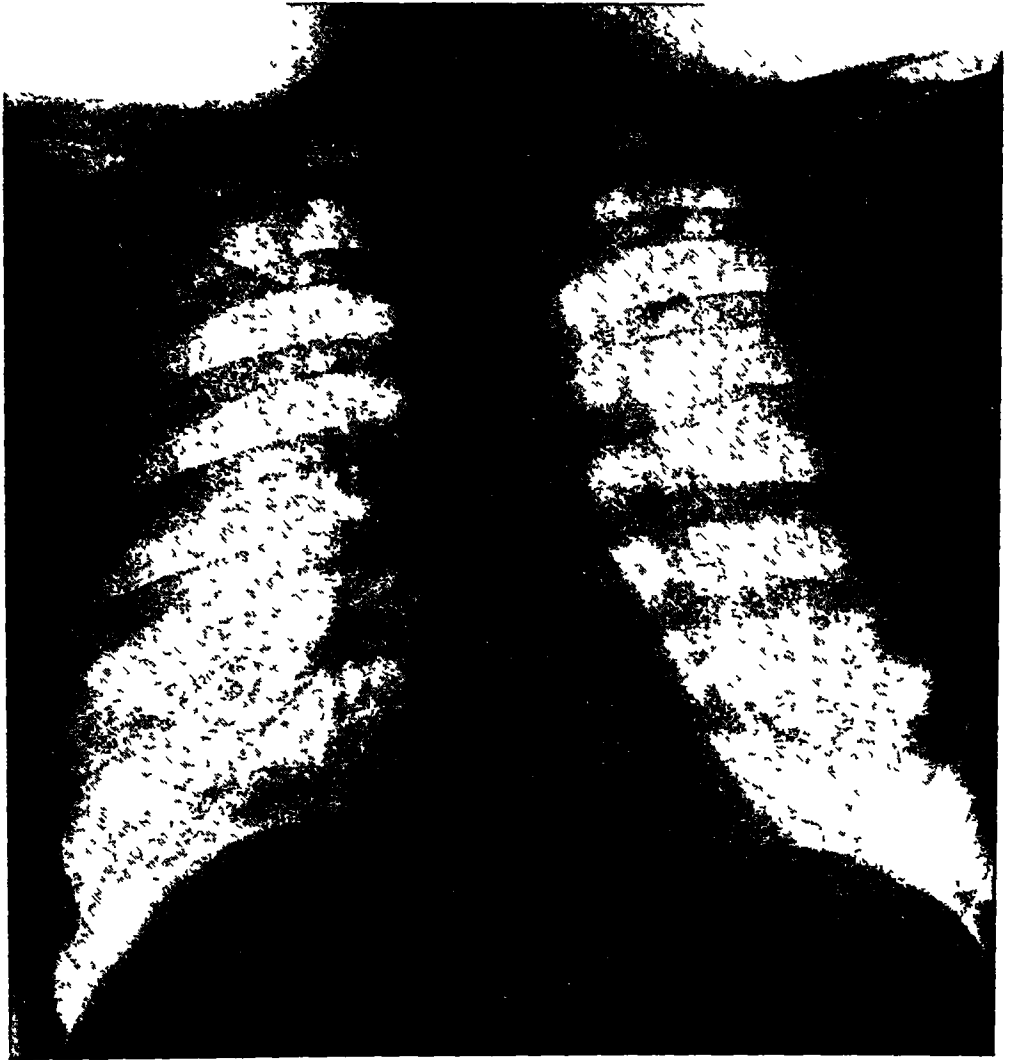


FIG 11 *Case V* Dr H E W February 6, 1930 Complete disappearance of cavity, with only fibroid scars remaining

rest sanatorium care, with all which that implies I am not disposed to enter into debate about the relative merits of home and sanatorium régime. I am so definitely convinced of the superiority of the sanatorium that I feel most of the objections thereto are academic, and I think this expresses the view very widely held by most men doing tuberculosis work Naturally, what happens in a given case depends largely upon the time at which the

disease is recognized as well as the extent and the kind of involvement. Far advanced, bilateral disease, with marked proliferative changes and destructive lesions, offer scant hope of more than amelioration at best, no matter what treatment is pursued. Yet here I should like to state one conviction that grows with the years in tuberculosis work—that astonishing things will happen in apparently hopeless cases with sufficient frequency to warrant the statement that every patient with any measure of reserve left should be given the benefit of careful observation before an utterly hopeless prognosis is pronounced. I do not feel that an extensive, one-sided tuberculosis, even with definite cavitation discovered at my first examination, is warrant necessarily for immediate compression therapy. I do feel that such a finding is an indication of delayed diagnosis, whosever the fault, rather than one for surgery. That such conditions heal very frequently without compression of any sort I have frequently seen demonstrated in my patients (Cases 1 to 5, figures 1 to 11). The process of repair is largely a matter of absorption and resolution and to a lesser extent of fibrosis. It is now fairly generally recognized that the symptoms which bring the patient to treatment for tuberculosis are the result of fairly fresh invasions of the bacillus into allergized fields in the lungs. As such, a good part of the pathologic process then represents an exudative or inflammatory lesion. Such lesions, unless quite virulent and aggravated by physical activity on the patient's part, quite frequently resolve under *proper rest*. Will caseous lesions heal? Here we come upon a vexed and difficult problem. The first difficulty is one of definition or, perhaps better, of interpretation. Certainly, lesions which give the physical signs indicative of caseation and the roentgenological appearance thereof (as we at present use these terms) can be seen to melt away and disappear in the serial films. Again, caseous lesions can be replaced by fibrosis, and certainly many so-called fibrous lesions in the films are seen to change and disappear, so that either fibro-caseous lesions resolve, or the time has come to clarify and change our nomenclature or conceptions of tuberculous pathology.

What of the cavity? Can it heal unless compressed? Undoubtedly, and in a great many more instances than could even have been hoped for some years ago. The interpretation of annular shadows may at times be open to question but in many instances in which these rings in the films were accompanied by unequivocal evidence in the patient of the presence of a cavity they have been seen to disappear without resort to any sort of compression therapy. Coryllos' recent observations, before the last meeting of the National Tuberculosis Association, upon the rôle of atelectasis in tuberculosis, are here much to the point. It may well be that atelectasis is produced not infrequently by closure of the bronchus leading into a cavity. There may be no harmful accumulation of sputum, and the resulting anaerobic state may exert a direct inhibiting effect upon the tubercle bacillus, which is a well known aerobe. It is possible that anoxemia stimulates fibrosis. Certainly all clinical observation has proved that the two methods

of healing in tuberculosis, resolution and fibrosis, can and do go on simultaneously, though not necessarily *pari passu*

Occasionally a patient on the dietetic, hygienic rest treatment alone achieves an astonishing cure by enormous fibrous and calcium deposits. How this last is accomplished I cannot say. Certainly, it is not so fortuitous a method of cure as resolution for reasons too obvious to mention, nor do blood calcium studies throw any particular light on the subject. Certainly raising the patient's blood calcium has not produced such a result.

If a patient under sanatorium care for three to six months at complete bed rest fails to gain or shows evidence of extension of his lesion, if the major lesions are fairly well confined to one lung, if there are no contra-indicating complications of tuberculous or other nature, then I think some form of compression therapy is indicated. First, I try pneumothorax, because it is safe, because it can usually be controlled and stopped if necessary, because its major disadvantages can be minimized with care, because it is not shocking, because its benefits are usually so apparent to the patient that he is easily convinced of its value, and because its results are frequently brilliant. Should pleural union prevent the injection of air or a satisfactory collapse, then I usually resort to phrenicectomy. Though certain cavities may be held open by string-like pleural bands, these may be severed after the manner of Jacobaeus or Matson, and a satisfactory collapse be obtained. Persistence of an open cavity and bacillary sputum, after such a procedure in a patient whose lesions are chiefly unilateral, whose general physical condition is good and whose circulatory system is competent, may then indicate the need of either apicolysis, tamponade, or thoracoplasty, as decided upon by the surgeon-internist team.

THE EFFECT OF PILOCARPINE ON THE VOLUME, FREE AND COMBINED ACID, TOTAL CHLORIDES AND PEPSIN OF GASTRIC SECRETION; AND A COMPARISON WITH THE EFFECTS OF HISTAMINE STIMULATION*

By LEO J MEIENBERG, M D , and CHARLES L BROWN, M D , F A C P ,
Ann Arbor, Michigan

A STUDY of the effect of pilocarpine on the various constituents of the gastric juice has been made. The results have been compared with those obtained following histamine stimulation.

MATERIAL

Studies were made in 13 cases. These included four normal people, four cases of pernicious anemia, two duodenal ulcers, one gastric carcinoma and two functional cases.

METHODS

All subjects were studied under fasting conditions, the fast beginning after the evening meal on the previous day. A Rehfuß tube with an olive tip was used for aspiration. A method of continuous aspiration by means of a water pump was employed, as described by Engelbach and Brown.¹ Care was taken that no saliva was swallowed by the patients during the test and in the event that the juice became bile-tinged the test was discarded. Sievers and Cook,² as well as others, have demonstrated that practically complete evacuation of the gastric contents was obtained by means of the Rehfuß tube. In view of this fact it was felt that quantitative studies based on the volume of secretion could be made, inasmuch as continuous aspiration was employed which would prevent any appreciable loss through the pylorus.

The fasting juice was collected for a period of at least 15 minutes in all tests. In eight cases histamine was then given hypodermically and the gastric juice collected for an hour, and in these cases this was followed by a hypodermic injection of pilocarpine and the collection of juice for another hour. In the other five cases pilocarpine was given first and an hour's secretion collected, followed by histamine in the same manner. Nothing was given by mouth during these periods. Pollard^{3, 4} has shown that the effect of histamine stimulation of gastric secretion ceases within an hour's time, and we were able to confirm this observation in our preliminary experiments with both histamine and pilocarpine. Thus it seems probable

* Received for publication April 12, 1933.

From the Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan.

TABLE I
This Table Shows the Volume, Acidities, Total Chlorides, Peptic Activity, and Total Peptic Activity of the Various Specimens

Case Number	Age	Weight Pounds	Sex	Volume			Free HCl			Total Acid			Total Chlorides			Pepsin Total Activity			Pepsin Maximum Activity per c c		
				F	II	P	F	H	P	F	H	P	F	II	P	F	II	P	F	H	P
Normal Individuals																					
5	24	145	M	13	195	21	28.4	37.0	41.4	37.1	41.4	50.1	75.6	84.8	91.6	4312.1	99255	10126.2	331.7	509	482.2
6	24	145	M	44	85	52	—	48.8	43.6	15.3	55.3	54.4	80.2	84.8	102.2	9719.6	44319	22656.4	220.9	521.4	435.7
7*	25	175	M	22	21	130	14.2	15.2	26.2	44.7	26.1	34.9	75.6	95.8	77.0	11814	19336.8	62010	537	920.8	477
8*	24	150	M	50	116	200	—	43.6	8.7	13.8	54.4	17.4	89.6	80.2	61.4	9050	43674	59260	181.0	376.5	296.3
Pernicious Anemia																					
3	59	100	F	7	2.5	19	—	—	—	not estimated	not estimated	not estimated	not estimated	not estimated	not estimated	889.7	293	3426.1	127.1	117.2	313.9
4	56	132	F	0	7	6	—	—	—	not estimated	not estimated	not estimated	not estimated	not estimated	not estimated	—	3266.2	1791.6	—	464.9	298.6
9	55	88	F	24	31	21	—	—	—	4	4	4	94.4	108.4	110.0	—	—	—	—	—	—
10*	48	140	M	16	21	21	—	—	—	4.4	4.4	2.0	92.8	51.8	45.6	281.6	2070.6	695.1	17.6	98.6	33.1
Duodenal Ulcer																					
2	35	119	M	33	72	35	26.2	56.1	42.6	32.7	66.6	54.5	114.6	133.3	142.4	9840.6	35172.0	19944.2	298.2	533.1	658.9
11	45	145	M	20	81	120	—	12.9	8.6	8.6	27.9	22.6	83.2	77.0	67.6	11312	69684.3	62004.3	565.6	860.3	516.7
Carcinoma of Stomach																					
13*	64	110	F	6	76	170	—	—	—	not estimated	not estimated	not estimated	not estimated	not estimated	not estimated	492	988	680	61.0	13.0	4.0
Functional Disease																					
1	14	86	F	15	55	19	32.7	65.5	67.6	39.4	72.1	80.7	118.0	126.4	143.8	5299.5	18309.5	6836.2	353.3	332.9	359.8
12*	34	129	F	110	45	110	28.9	34.4	35.4	42.9	50.5	41.8	not estimated	not estimated	not estimated	52723	38074.5	101695.0	479.3	846.1	924.5
* Pilocarpine given first 20'-30' specimen only																					
F = Fasting specimen H = After histamine (1 hour period) P = After pilocarpine (1 hour)																					

* Pilocarpine given first 20'-30' specimen only

F = Fasting specimen
H = After histamine (1 hour period)

P = After pilocarpine (1 hour)

that the secretion obtained during our second hour was not influenced by the drug which was given first

The dosage of histamine phosphate used was 0.1 mg per 10 kg of body weight, while pilocarpine nitrate was given in dosages of 0.5 mg per 10 kg of body weight

The gastric juice was collected and studied in three fractions which were designated *fasting*, *after pilocarpine* and *after histamine*

In this manner, in addition to estimating the stimulating effect of these drugs in terms of the maximum concentration during a given period, quantitative determinations of pepsin and volume secretion were estimated, also the acidity and total chlorides were determined on the fractions and the quantities of each of these for the period could be calculated. This would seemingly offer a quantitative index of gastric function

The volume of each specimen was measured. Free and total acidities were estimated by means of Topfer's dimethyl indicator and phenolphthalein. Total chlorides were determined by the method of Van Slyke⁵ and pepsin estimations were made according to the method of Pollard and Bloomfield⁶. In the latter determination the peptic activity per c.c. was multiplied by the volume of the specimen in c.c. to obtain total peptic activity. This figure was used as a basis of comparison also, in addition to the values for maximum peptic activity per c.c.

TABLE II

PEPTIC ACTIVITY

This Table Shows Volume in c.c. (A) of the Various Specimens, Peptic Activity Expressed as Mg. Edestin Digested per c.c. of Gastric Juice, (B), and Total Peptic Activity as Obtained by Multiplying the Former Two, (A × B)

Case	Diagnosis	Volume (A)			Mg. Edestin digested per c.c. gastric juice (B)			Total Peptic Activity (A × B)		
		F	H	P	F	H	P	F	H	P
5	Normal	13	195	21	331.7	509	482.2	4312.1	99255	10126.2
6	Normal	41	85	52	220.9	521.4	435.7	9719.6	44319.0	22656.4
7	Normal*	22	21	130	537	920.8	477	11814	19336.8	62010.0
8	Normal*	50	116	200	181	376.5	296.3	9050	43674	59260.0
3	Pernicious anemia	7	2.5	19	127.1	117.2	313.9	889.7	293.0	3426.1
1	Pernicious anemia	0	7	6	—	464.9	298.6	—	3266.2	1791.6
9	Pernicious anemia	24	31	21	—	—	—	—	—	—
10	Pernicious anemia*	16	21	21	17.6	98.6	33.1	281.6	2070.6	695.1
2	Duodenal ulcer	33	72	35	298.2	533.1	658.9	9840.6	35172.0	19944.2
11	Duodenal ulcer	20	81	120	565.6	860.3	516.7	11312	69684.3	62004.3
12	Cancer of stomach*	6	76	170	61	13.0	4.0	492	988.0	680
1	Functional disease	15	55	19	353.3	332.9	359.8	5299.5	18309.5	6836.2
13	Functional disease*	110	45	110	479.3	846.1	921.5	52723	38074.5	101695.0

* Pilocarpine given first
 F = Fasting,
 H = After histamine,
 P = After pilocarpine

ANALYSIS OF RESULTS

Volume In the four normal cases, whichever drug was used for the first hour's stimulation produced a very definitely greater volume. In one instance this ratio was greater than 9:1. With the four cases of pernicious anemia, the volume was approximately the same for both drugs regardless of which was studied first. There was one exception, in which the quantities were small, but in which the second drug given (pilocarpine in this instance) produced a greater volume of juice. In the two cases of duodenal ulcer, one responded better to histamine and one better to pilocarpine though both patients received histamine first. In the other cases as in the normals, the first stimulant gave the best response. When all cases were considered it was apparent that pilocarpine stimulation produced a greater volume than histamine stimulation.

Free and Total Acid There was very little difference in the concentration of acid when the results during the two periods of stimulation were compared, regardless of which drug was given first. Only in one normal subject was there a definite response favoring histamine.

Total Chlorides The greater concentration of chlorides practically always occurred with the smaller volume, regardless of which drug was used for stimulation.

Pepsin In the normal subjects the greatest peptic activity per c.c. always followed histamine stimulation regardless of which drug was given first. When the total peptic activity (volume of spec. in c.c. x peptic activity per c.c. expressed as mg. Edestin digested) was considered, the greatest values were found following the drug which was used as the first stimulant. This also corresponded with the greater volume of secretion. In these cases the peptic activity per c.c. following histamine was always greater than the fasting value. The figures following pilocarpine were also definitely greater than the fasting values with one exception, in which instance a very large volume of juice was secreted after pilocarpine stimulation.

In the four cases of pernicious anemia which were studied, one patient gave no evidence of pepsin secretion, one responded better to pilocarpine and two better to histamine. In each of the last three cases the histamine was given first. These values expressing peptic activity were also definitely higher than the fasting values. The figures for total peptic activity were comparable with those for peptic activity per c.c.

One ulcer patient had greater evidence of peptic activity per c.c. following pilocarpine while the other had a higher value following histamine. The total peptic activity was higher in each case following histamine, however, it was the first drug administered in both instances.

In the one case of carcinoma of the stomach, the peptic activity per c.c. was higher in the fasting specimen than in those following histamine and pilocarpine stimulation. The peptic activity per c.c. and the total peptic activity were greater following histamine stimulation than after pilocarpine,

though the latter was given first and the volume of pilocarpine secretion was more than twice as great

There was no marked difference in peptic activity per c c in the functional cases following histamine and pilocarpine though when total activity was considered the higher values were associated with the larger volumes

DISCUSSION

The effect of pilocarpine on the gastric secretion has been previously studied on numerous occasions, though we are aware of no previous study on humans taking into account quantitatively the various elements of the gastric juice. Moreover, the results obtained by the various investigators have not been comparable. The preponderance of opinion seems to have been that pilocarpine caused no increase and perhaps depressed the gastric acidity. Altshuler⁷ in 1928 reviewed the previous work, and reported some original studies but determined only the free and total acidity on humans. He also studied the effects of atropine and epinephrine on the gastric secretion. Schwab⁸ and Mitrovitch⁹ independently concluded that a decrease in acidity resulted following the use of pilocarpine. The former was of the opinion that this effect was not due to an increased secretion of gastric mucus and the latter felt that the action of pilocarpine was very similar to that of atropine in inhibiting the gastric secretion.

Vineberg and Babkin¹⁰ in 1931 suggested the use of pilocarpine with histamine as a test of gastric function on the basis of their experimental work with dogs. They concluded that histamine stimulated the secretion of water, hydrochloric acid and other inorganic constituents without affecting enzyme action. Pilocarpine on the other hand tended to stimulate the secretion of enzymes. Because of these findings they pointed out that a "combination of histamine and pilocarpine produces a synthetic gastric juice approaching normal."

Gilman and Cowgill¹¹ also maintained that histamine did not stimulate the secretion of pepsin, their work also was done on dogs.

Polland³ on the other hand concluded that histamine did stimulate the secretion of pepsin.

It has been shown by Engelbach and Brown¹ that the gastric secretion in its response to histamine is not constant from day to day. For this reason it was thought that a better comparison between the actions of histamine and pilocarpine could be made if successive hourly periods were studied. While this method does not seem to give perfectly comparable results, as the response during the second hour in some cases apparently was diminished, it seems that some very definite information was obtained.

It is evident from the tables that the greater total peptic activity does not necessarily occur in the specimen where the greater peptic concentration is obtained. (See Cases 7, 8, 2, 1). The digestive power of gastric juice under standard, optimal conditions is dependent upon the amount of pepsin

present Because of these facts we feel that a better quantitative index of peptic activity can be obtained if the volume of gastric secretion during a given period is considered

SUMMARY

It has been demonstrated that pilocarpine is a true stimulant of gastric secretion, its chief effect being an increased volume of gastric juice, the acid and pepsin secretions, however, are also stimulated Histamine also stimulates the secretion of pepsin, and the values obtained are not explained by a process of washing out of the gastric crypts as suggested by some workers

No definite evidence is obtained to support the opinion expressed by some experimenters that pilocarpine is a better stimulant of enzyme secretion than histamine The results are not sufficiently conclusive to say that either is a better stimulant for enzyme secretion than the other This also seems to be true in regard to the secretion of acid There is no appreciable difference in the effect of these two drugs on the secretion of total chlorides

No untoward symptoms were noted from the use of pilocarpine in the doses given, with the exception of slight nausea which was experienced by one patient A definite increase in salivation was noted in practically all cases

The estimation of total peptic activity during a given period would seem to be a better quantitative index of peptic secretion than a determination of the concentration of pepsin

CONCLUSIONS

- 1 Pilocarpine is a stimulant of gastric secretion, as shown by its effect on the volume, acidity, chlorides and pepsin content of the gastric juice
- 2 Histamine stimulates the secretion of pepsin
- 3 No evidence is obtained that pilocarpine is more effective in the stimulation of pepsin secretion than is histamine
- 4 Histamine has not been proved to be a definitely better stimulant of gastric secretion than pilocarpine as determined by the volume, acidity, total chlorides and pepsin content of the gastric juice

BIBLIOGRAPHY

- 1 ENGELBACH, F, and BROWN, C L Variations in the volume and in the acid content of gastric secretion of normal individuals following stimulation by histamine, ANN INT MED, 1933, vi, 1560-1564
- 2 SIEVERS, E F, and COOK, J E Competency of Rehfuess tube as complete evacuator, Jr Lab and Clin Med, 1932, xvi, 1120-1123
- 3 POLLAND, W S Stimulation of gastric pepsin by histamine, Jr Clin Invest, 1932, xi, 449-454
- 4 POLLAND, W S Effect of atropine upon gastric secretion after histamine stimulation, Jr Clin Invest, 1930, ix, 319-332
- 5 VAN SLYKE, D D Determination of chlorides in blood and tissues Jr Biol Chem, 1923, lvi, 523-529

- 6 POLLAND, W S, and BLOOMFIELD, A L Quantitative method for estimation of pepsin, *Jr Clin Invest*, 1929, vii, 45-55
- 7 ALTSHULER, A M Gastric secretion, its alteration by use of atropine, epinephrine and pilocarpine, *Arch Int Med*, 1928, xlii, 117-134
- 8 SCHWAB, E Die Wirkung einzelner Arzneimittel auf die Magenfunktion unter gleichzeitiger Berücksichtigung von Blutdruck, Puls und Blutbild, Pilocarpinwirkung, *Ztschr f d ges exper Med*, 1928, lxi, 163-180
- 9 MITROVITCH Action of pilocarpine on the stomach, *Comp rend Soc d biol*, Abstr, *Jr Am Med Assoc*, 1926, lxxxvi, 1402
- 10 VINEBERG, A M, and BABKIN, B P Histamine and pilocarpine in relation to the gastric secretion, *Am Jr Physiol*, 1931, xcvi, 69-73
- 11 GILMAN, A, and COWGILL, G R Effect of histamine upon secretion of gastric pepsin, *Am Jr Physiol*, 1931, xcvi, 124-130

THE INCIDENCE AND SIGNIFICANCE OF THE SICKLE CELL TRAIT*

By L W DIGGS, M D , C F AHMANN, PH D , and JUANITA BIBB, A B ,
Memphis, Tennessee

IF ONE takes a drop of blood from each member of an unselected series of negroes, seals the drops under cover-slips, and examines them microscopically over a period of hours, he observes striking curved and pointed distortions of the erythrocytes in an appreciable number of the preparations (Figure 1) Erythrocytes assuming such bizarre stellate shapes are called "sickled cells" and individuals whose erythrocytes are capable of undergoing such a metamorphosis under suitable conditions are said to possess the "sickle cell trait" The anomaly is hereditary and is thought to be transmitted as a dominant Mendelian characteristic Within the large group of those who inherit the sickle cell trait, an undetermined number, due to factors unknown, develop varying degrees of "sickle cell anemia," a hemolytic type of blood dyscrasia with characteristic clinical and pathological features

Estimations of the frequency of occurrence of the sickle cell trait have been recorded by a number of observers, but the number of individuals examined has been relatively few, most of the studies have been made on hospital patients, and little attention has been given to the variable factors which play a part in the detection of the anomaly The clinical importance of the sickle cell trait in absence of anemia, and the relationship of the trait to sickle cell anemia are subjects of controversy For these reasons, it seems justifiable to present evidence revealed in our investigations which deals with the incidence and significance of the sickle cell trait

METHOD

The individuals included in the surveys reported in this article were taken at random from groups of normal and hospital negroes and white people One series examined by Ahmann consisted of negro school children and teachers in the grammar and high schools of Gainesville, Florida Another series consisted of hospital negroes in the medical, surgical, obstetrical and pediatric wards, and in the out-patient clinic of the Memphis General Hospital, and in the medical wards of the Shelby County Hospital, Memphis, Tennessee The white subjects examined for the presence of the sickle cell trait were medical students of the University of Tennessee and medical patients of the Memphis General Hospital

Sealed moist preparations, used throughout the study as a means of detection of the sickle cell anomaly, were made in the following manner

* Received for publication March 31, 1933

From the Department of Clinical Pathology, University of Tennessee, Pathological Institute, Memphis, Tennessee, and from the Nutritional Division of the Experimental Station, University of Florida, Gainesville, Florida

In the school series, new slides and new No 0 and No 1 cover-slips were boiled in cleaning solution, rinsed in distilled water and 95 per cent alcohol, then left in a mixture of alcohol and ether until dried for use. In the hospital series new slides and new No 1 and No 2 cover-slips were used. The method of cleaning varied, most of the glassware, however, was washed for 24 hours in running tap water and placed in 95 per cent alcohol, until dried for use. Capillary blood from alcohol cleaned fingers or heels was used for

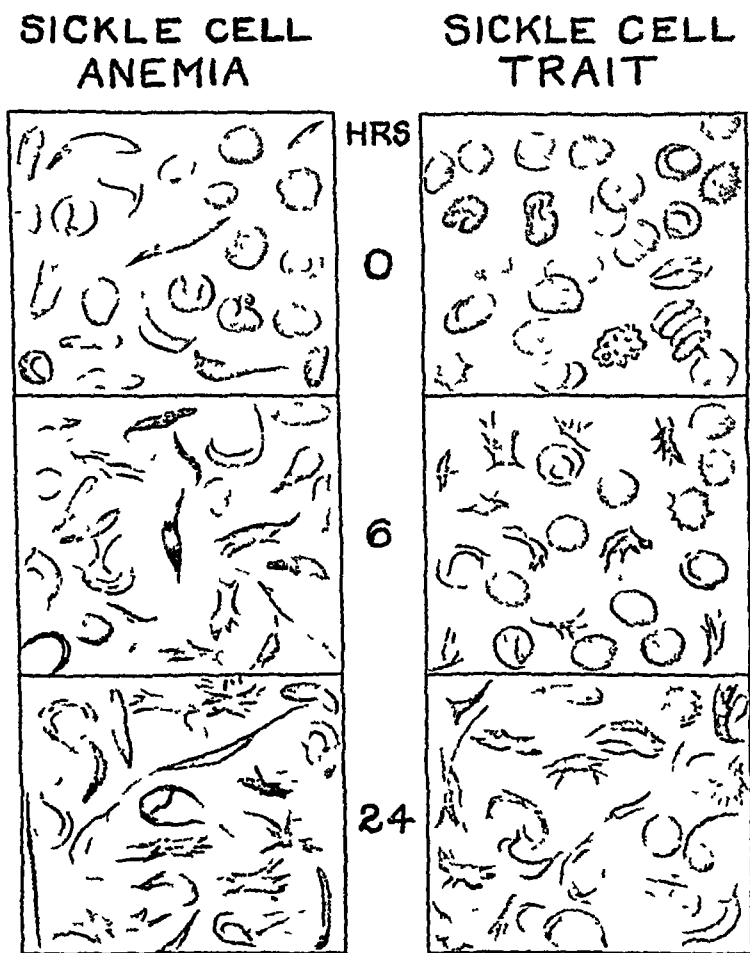


FIG. 1 Drawing showing the morphology of sickled erythrocytes in sickle cell anemia and in the sickle cell trait as revealed in sealed moist preparations at the time of making the preparations and after six hours and after 24 hours

all preparations with the exception of those made in the out-patient department, where venous blood drawn for routine Wassermann tests was utilized. A small drop of blood was taken on a cover-slip, and the cover-glass placed drop-side down on a slide. The blood was allowed to spread without pressure, after which the edges of the cover-glass were rimmed with petrolatum. In the first 500 cases only one moist preparation was made per patient, but in the remaining hospital cases and in all of the school cases, two preparations per patient were made. The sealed drops were left at room temperature

and examined under high dry magnification four times, once immediately after returning to the laboratory, and at 24 hour intervals thereafter for three days. The sickle cell trait for a given individual was recorded as positive when definite long tapering filaments and typical sickle cell distortions were observed. Crenated cells, elliptical cells, cells with blunt filaments and poikilocytosis of a questionable and non-specific nature were not considered as manifestations of the sickle cell phenomenon.

RESULTS

The number of negroes examined in the hospital series was 2,539, of which number 211 or 8.3 per cent were demonstrated to have sickled cells in moist preparations. Of 674 negro school children and teachers examined, the sickle cell phenomenon was observed in 65 or in 9.6 per cent of the preparations. By combining our series with those previously recorded in the literature,¹⁻¹¹ the average frequency of demonstration of the trait in negroes is found to be 7.3 per cent (619 in 8,453) (Table 1). It is probable that the real incidence of the sickle cell trait is higher than this demonstrated average, because most of the sources of error in the method are on the side of not detecting the trait when it is present rather than in making false positive diagnoses.

Moist preparations were made with the blood of 309 white people and in no preparation was there any evidence of sickle cell distortion. Other sur-

TABLE I
Incidence of the Sickle Cell Trait
Negroes

Author	Place	Number Examined	Number with Trait	Per cent with Trait
Sydenstricker, Mulherin and Houseal	Ga	300	13	4.3
Cooley and Lee	Mich	400	30	7.5
Miyamoto and Korb	Mo	300	19	6.3
Wollstein and Kreidel	N Y	150	13	8.6
Josephs	Md	250	16	6.4
Smith	La	100	5	5.0
Dolgopel and Stitt	N Y	77	4	5.2
Levy	N Y	213	12	5.6
Graham and McCarty	Ala	1,500	122	8.1
Brandau	Tex	150	10	6.7
Sydenstricker	Ga	1,800	99	5.5
Diggs, Ahmann and Bibb	Tenn	2,539	211	8.3
Ahmann	Fla	674	65	9.6
Total		8,453	619	7.3
<i>Whites</i>				
Sydenstricker	Ga	1,000	0	0.0
Miyamoto and Korb	Mo	100	0	0.0
Diggs, Ahmann and Bibb	Tenn	309	0	0.0
Total		1,409	0	0.0

veys of white people have likewise yielded negative results ^{3,12} (Table 1) The series reported by Lawrence,¹³ which is falsely interpreted by some as being a proved demonstration of sickled erythrocytes in white people, is not included, for he describes and pictures elliptical cells and not true sickled cells Wollstein and Kreidel⁴ were unable to demonstrate the sickle cell phenomenon in white children, but fail to state the number examined

Isolated instances of the sickle cell trait in white people have been placed on record by Castana,¹⁴ Archibald,¹⁵ Stewart,¹⁶ Cooley and Lee,¹⁷ Sights and Simon,¹⁸ and by Rosenfeld and Pincus¹⁹ There is reason to suspect negro blood in the cases reported by Archibald and by Stewart The claims of Castana and of Sights and Simon are contestable because of inadequate investigation of the families and because they did not prove conclusively by word description or illustration that they were dealing with the sickle cell trait Cooley and Lee presented evidence of the sickle cell phenomenon in a Greek family, and Rosenfeld and Pincus demonstrated the presence of sickled cells in an Italian family In both of these families there was no evidence of mixed blood From these observations it is evident that the sickle cell trait is frequent in the negro race and quite rare in the white race, and that clearly established cases among white people have been limited to those of Mediterranean stock If the sickle cell trait is a dominant characteristic, there will come from the interbreeding of the races an increasing number of cases with the sickle cell trait in those apparently white¹⁹ Whether or not the trait occurs in pure white strains will long remain a disputed point, and will be settled by preponderance of evidence rather than by single cases

Examination of table 1 reveals slight differences in the incidence of the sickle cell trait as recorded by different observers, which is to be expected in any frequency estimation which deals with relatively small series and with many variable factors Climate and geographical location do not seem to be important factors, as there are no significant or constant variations in the incidence in the widely separated localities where surveys have been conducted

An analysis of the incidence according to sex discloses an even distribution of the sickle cell trait in males (8.4 per cent) and in females (8.1 per cent) (Table 2)

An examination of the series to determine the incidence of the sickle cell trait according to age reveals the following findings The lowest percentage occurred in new born babies, the sickle cell trait being demonstrated in only 3.1 per cent (6 in 159) It was also noted that the sickle cell distortion in this group was less marked and developed more slowly than in adults with the trait In the negro school children the sickle cell phenomenon was demonstrated in 8.6 per cent (24 in 270) of those from 6 to 10 years of age, in 9.7 per cent (27 in 277) of those 11 to 15 years of age, and in 11.2 per cent (13 in 115) of the 16 to 20 year old group This slight increase in incidence with advancing years is probably not significant The

TABLE II
Incidence of the Sickle Cell Trait According to Sex
Females

Author	Number Examined	Number with Trait	Percentage
Miyamoto and Korb	196	14	7.1
Graham and McCarty	944	72	7.7
Diggs, Ahmann and Bibb	1,297	106	8.2
Ahmann	394	38	9.7
Total	2,831	230	8.1

Males

Miyamoto and Korb	104	5	4.8
Graham and McCarty	556	50	8.7
Brandau	150	10	6.6
Diggs, Ahmann and Bibb	1,162	97	8.3
Ahmann	280	27	9.6
Total	2,252	189	8.4

frequency of demonstration of the sickle cell trait according to age for the entire group of negroes examined, including both the hospital and school series, is given in figure 2

The youngest negro found to have sickled erythrocytes was a premature infant, and the oldest was 99 years of age. Twelve negroes who remembered incidents of slave days and the Civil War were still with us in spite of the sickle cell trait, which is rather definite evidence that the anomaly is compatible with life even beyond the period of life expectancy. These observations are not consistent enough to lead to very definite conclusions, but they suggest that the trait is least demonstrable in moist preparations in the newly born, most frequently observed in childhood and tends to decrease slightly with advancing years.

NUMBER EXAMINED	159	158	386	417	309	267	252	183	157	135	158	105	122	136
NUMBER WITH TRAIT	6	18	39	39	30	27	23	12	14	11	9	7	9	12

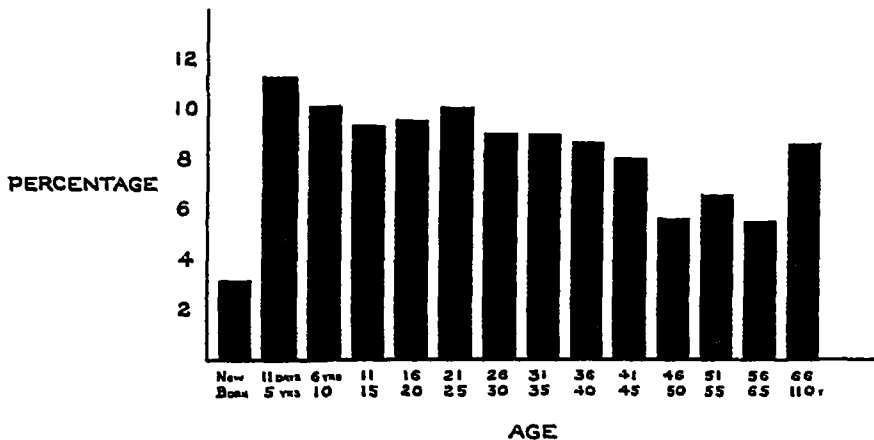


FIG 2 The incidence of demonstration of the sickle cell trait in negroes according to age

An evaluation of the effect of the mixture of white and negro blood on the incidence of the sickle cell trait was attempted by noting the frequency of occurrence of the trait in light and very light negroes as contrasted with dark and black types. It was found that 13.1 per cent (27 in 206) of the lightly pigmented negroes possessed the trait, whereas the percentage incidence in a comparable series of the deeply pigmented negroes was 7.1 per cent (51 in 701). The finding of an apparently significantly higher incidence in negroes with mixed blood than in pure negroid types must be confirmed before we speculate as to its cause, but it suggests avenues for further investigation.

In order to determine the effect of the state of health on the incidence of the sickle cell trait, comparisons were made of the frequency of occurrence of the trait in healthy negro school children and in hospital children of the same age. It was found that the incidence in the school series was 9.7 per cent (64 in 662) and in the hospital series the incidence was 9.8 per cent (44 in 450). These two series are not entirely comparable in that the examinations were made in different localities and the technic used was not exactly the same. Sydenstricker¹¹ demonstrated the sickling trait in 5.5 per cent of 1,800 presumably healthy negro children in the public schools, and Brandau¹⁰ found that 6.7 per cent of 150 negro applicants for industrial work possessed the sickle cell trait. These figures are within the range of variation of similar series reported on hospital patients. From these findings we may conclude that a higher incidence of the sickle cell trait among sick negroes than among the healthy remains to be proved.

That the method of collection of blood may have an effect on the demonstrability of sickled cells is suggested by the fact that in a series of 823 preparations made with venous blood, sickled cells were observed in 10.2 per cent while in 1,716 preparations made with capillary blood the incidence was 7.4 per cent. It was found that the weight of the cover-slip was not a factor of importance in the determination of the sickle cell trait. Series of preparations made on the same patients, using No. 1 and No. 2 cover-slips, revealed a slower and a less complete development of the sickling phenomenon under the heavier cover-slip within the first few hours, but at 24 hours there was no consistent difference.

THE SIGNIFICANCE OF THE SICKLE CELL TRAIT

A review of the literature dealing with the significance of the sickle cell trait shows that early workers^{20, 21} considered the demonstration of sickled cells to be of definite clinical importance, but with increasing knowledge the general trend of opinion has been to assign to the sickle cell trait less and less significance. It is now generally conceded that the diagnosis of the sickle cell trait in absence of anemia can only be made by use of special methods such as the moist preparation or gas chamber, and that the history, physical signs and ordinary laboratory procedures do not give information which can be relied upon for recognition.^{9, 10, 22, 23} Although many opinions have been

expressed as to the significance of the sickle cell trait, there are few facts and figures. Observations made in our studies may elucidate certain disputed points.

Greenish-yellow discoloration of the sclerae is a common finding in patients with sickle cell anemia and is thought by some to be also characteristic of the sickle cell trait. The sclerae were examined in 438 negroes in our series on whom moist preparations were made. It was found to be extremely difficult accurately to describe the combinations of pigmentary change encountered. The sclerae of many individuals had background colors of gray, slate and brown, which were further complicated by black and brown macules, by dilatation of superficial vessels giving red appearances and by pingueculae. The sickle cell phenomenon was demonstrated in 28 and absent in 313 negroes who were considered to have scleral tints of green and of yellow. In 97 negroes with no definite discoloration, six were found to have sickled cells. From these investigations we come to the definite conclusion that the color of the sclerae in negroes cannot be used as a diagnostic aid in the detection of the sickle cell trait.

In order to determine whether patients with the sickle cell trait had leg ulcers more commonly than did those without the trait, the legs of 304 negroes were examined at the time moist preparations were made. It was noted that many negroes had scars and pigmentary changes of some kind on their legs, most of which could be accounted for by the trauma of barefoot years, industrial pursuits and superficial burns from huddling around fireplaces and red hot stoves. Only those cases with definite rounded scars who gave a history of delayed healing were recorded as positive. No open lesions were found. Of 258 negroes with no scars of the type found in sickle cell anemia, 21 (8.1 per cent) possessed the sickle cell trait, whereas within the group of 46 negroes with suspicious scars there were four negroes (8.7 per cent) in whom sickled cells were demonstrated. Although this series is too small and the criteria for judging the ulcerations too indefinite to draw conclusions, it does not support the idea that leg ulcers occur more commonly in those with the sickle cell trait than in normal individuals.

It has been generally assumed that negroes with the sickle cell trait have a tendency to develop anemia, but there is little evidence to support this idea, beyond the fact that a few have sickle cell anemia. Cooley and Lee² stated that "moderate anemia seems to be the rule among our colored children, and that there is practically no difference in this regard between those with and without sickled cells." Miyamoto and Korb³ came to the same conclusion. Josephs⁴ found no anemia in 16 children with characteristic sickle cell changes. In order to determine in a normal group whether or not those with the sickle cell trait were more anemic than those without the trait, hemoglobin determinations by the Dare method were made on 672 negro school children. Of 65 cases found to have the sickle cell trait, the highest hemoglobin reading was 103 per cent, the lowest 60 per cent and the average for the group 82.6 per cent. In the series of 607 without the trait, the

highest hemoglobin was 108 per cent, the lowest 60 per cent and the average 81.4 per cent. Frequency distribution curves in percentage are given in graphic form (Figure 3). These findings indicate that the majority of individuals with the sickle cell trait are no more anemic than others in the same environment without the trait.

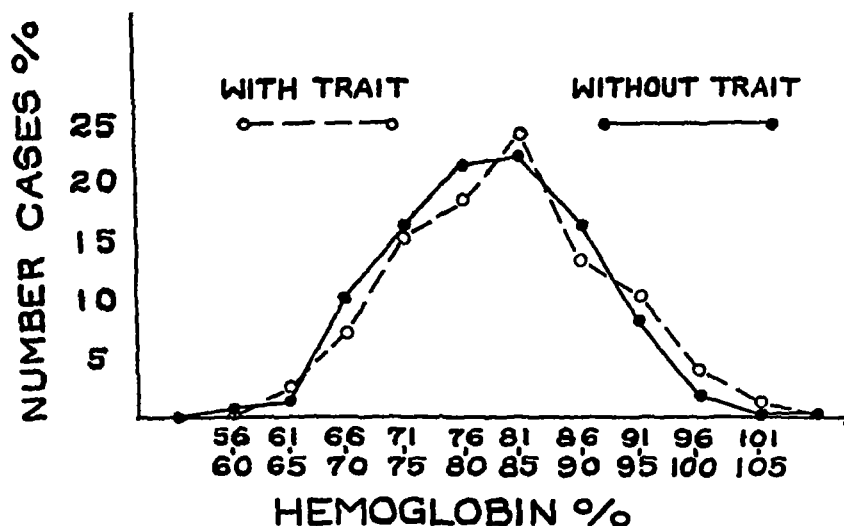


FIG. 3. Frequency distribution curve of hemoglobin determinations in 65 negro school children with the sickle cell trait and in 607 negro school children without the trait.

It is not as yet possible to estimate with any degree of accuracy how often sickle cell anemia develops within the group of those whose erythrocytes sickle. Severe cases of sickle cell anemia with characteristic symptoms and signs often are not recognized, and mild cases with less definite diagnostic signs are seldom detected. Sydenstricker²⁰ estimated that in hospital patients the ratio of anemia to the trait was one to nine. In a recent survey of school children, he found the ratio to be 1 to 50 and adds that "among children admitted to the hospitals and out-patient clinics the number is of course greater." On the medical and pediatric wards of the Memphis General Hospital during a 30 month period 14 cases of sickle cell anemia were recognized. Estimating the number of patients with the sickle cell trait as 7.4 per cent of the total number of admissions during the same period, the ratio of sickle cell anemia to the sickle cell trait is 1 to 40. These figures are merely rough estimates, but if approximately correct they indicate that sickle cell anemia is much more frequent than is commonly believed and that the number affected in the United States alone probably numbers in the tens of thousands.

SUMMARY AND CONCLUSIONS

1. The sickle cell trait was demonstrated by means of sealed moist preparations of whole blood in 83 per cent of 2,539 out-patient and hospital negroes examined at Memphis, Tennessee, and in 96 per cent of 674 negro school children and teachers at Gainesville, Florida.

2 The incidence of the sickle cell trait as demonstrated in moist preparations in the combined surveys reported in the literature and including the series reported in this paper is 7.3 per cent (619 in 8,453 examined).

3 The sickle cell trait has not been demonstrated in recorded surveys of white people, and the only reasonably proved instances of the sickle cell trait in families with unmixed blood have been limited to those of the Mediterranean stock.

4 Geographical location, sex and state of health do not appear to be factors affecting the incidence of the sickle cell trait.

5 In our series the frequency of demonstration of the sickle cell trait varied with age, degree of pigment and method of collection of blood, but the series are too small and the uncontrolled factors too numerous to draw definite conclusions.

6 That the sickle cell trait in absence of anemia is of little clinical significance is supported by the following observations:

(a) The trait is compatible with long life.

(b) The incidence in hospital cases has not been proved to be higher than in healthy individuals.

(c) Leg ulcers and greenish-yellow discoloration of the sclerae appear as frequently in those without the trait as in those with the trait.

(d) Hemoglobin determinations in a series of negro school children revealed parallel findings in those with and without the trait.

7 The ratio of sickle cell anemia to the sickle cell trait is estimated 1 to 40.

8 The importance of the sickle cell trait appears to be limited to the relatively small group who in addition to the trait have sickle cell anemia.

BIBLIOGRAPHY

- 1 SYDENSTRICKER, V. P., MULHFRIN, W. A., and HOUSEAL, R. W. Sickle cell anemia, report of two cases in children, with necropsy in one case, *Am Jr Dis Child*, 1923, xxvi, 132-156.
- 2 COOLEY, T. B., and LEE, P. Sickle cell phenomenon, *Am Jr Dis Child*, 1926, xxxii, 334-340.
- 3 MIYAMOTO, K., and KORB, J. H. Meniscocytosis (latent sickle cell anemia), its incidence in St. Louis, *South Med Jr*, 1927, xx, 912-916.
- 4 WOLLSTEIN, M., and KREIDEL, K. V. Sickle cell anemia, *Am Jr Dis Child*, 1928, xxxvi, 998-1011.
- 5 JOSEPHS, H. Clinical aspects of sickle cell anemia, *Bull Johns Hopkins Hosp*, 1928, xliii, 397-398.
- 6 SMITH, J. H., JR. Sickle cell anemia, *Med Clin N Am*, 1928, xi, 1171-1190.
- 7 DOLGOPOL, V. B., and STITT, R. H. Sickle cell phenomenon in tuberculosis patients, *Am Rev Tuberc*, 1929, xix, 454-460.
- 8 LEVY, J. Sicklemia, *ANN INT MED*, 1929, iii, 47-54.
- 9 GRAHAM, G. S., and MCCARTY, S. H. Sickle cell (meniscocytic) anemia, *South Med Jr*, 1930, xxiii, 598-607.
- 10 BRANDAU, G. M. Incidence of sickle cell trait in industrial workers, *Am Jr Med Sci*, 1930, clxxx, 813-817.
- 11 SYDENSTRICKER, V. P. Discussion of paper, *South Med Jr*, 1932, xxv, 620.

- 12 SYDENSTRICKER, V P Sickle cell anemia, *South Med Jr*, 1924, xvii, 177-183
- 13 LAWRENCE, J S Elliptical and sickle-shaped erythrocytes in the circulating blood of white persons, *Jr Clin Invest*, 1927, v, 31-49
- 14 CASTANA, V I Gigantociti e le Anemie Semilunari, *Pediatrics*, 1925, xxxiii, 431-440
- 15 ARCHIBALD, R G Sickle cell anemia in the Sudan, *Tr Roy Soc Trop Med and Hyg*, 1926, xix, 389-393
- 16 STEWART, W B Sickle cell anemia, report of case with splenectomy, *Am Jr Dis Child*, 1927, xxxiv, 72-80
- 17 COOLEY, T B, and LEE, P Sickle cell anemia in a Greek family, *Am Jr Dis Child*, 1929, xxxviii, 103-106
- 18 SIGHTS, W P, and SIMON, S D Marked erythrocytic sickling in a white adult associated with anemia, syphilis and malaria, report of case, *Jr Med*, 1931, xii, 177-178
- 19 ROSENFELD, S, and PINCUS, J B Occurrence of sickle anemia in white race, *Am Jr Med Sci*, clxxxiv, 674-682
- 20 SYDENSTRICKER, V P Further observations on sickle cell anemia, *Jr Am Med Assoc*, 1924, lxxxiii, 12-17
- 21 GRAHAM, G S, and McCARTY, S H Sickle cell anemia, *Jr Lab and Clin Med*, 1927, xii, 536-547
- 22 STEINBERG, B Sickle cell anemia, *Arch Path*, 1930, ix, 876-897
- 23 ANDERSON, W W, and WARE, R L Sickle cell anemia, *Jr Am Med Assoc*, 1932, xcix, 902-905

HEART BLOCK IN THE YOUNG *

By I I LEMANN, M D , F A C P , *New Orleans, Louisiana*

IT IS GENERALLY thought that heart block occurs exclusively in persons past middle age, chiefly in those of old age. A review of the literature of the past six years will soon yield a very different impression. I have been able to find in the literature reports of 99 cases of atrioventricular block occurring in patients below the age of 30. There are, in addition to these, several other titles in the literature to which I have not had access, or concerning which I am not certain. The probable number reported is, therefore, approximately 100. In five the diagnosis was made on clinical evidence only, in all the rest it was substantiated by electrocardiographic tracings or phlebograms. Some idea of the incidence of heart block in general, and in young people under 30 years of age, may be formed from the following. Paul White¹ states that, "in an electrocardiographic series of 9000 patients with cardiac symptoms or signs, atrioventricular block was diagnosed in 581 cases (6.5 per cent). Coronary disease was apparently responsible in 35 of another series of 69 cases of atrioventricular block (29.3 per cent), rheumatic infection in 19 (32.2 per cent), congenital defect in one, luetic involvement in one, digitalis medication in nine, and an unknown factor in four cases." In an electrocardiographic series of 3000 patients in Touro Infirmary we have had 38 cases of atrioventricular block, (11 complete block, 6 partial block, 21 delayed conduction time beyond 0.20 seconds). One of the complete blocks and one of the partial blocks were in patients aged 22 and 28, respectively. By courtesy of Dr. Richard Ashman I am permitted to quote the statistics of Charity Hospital, New Orleans. In 2825 patients with cardiac symptoms or signs, there were 264 patients with affections of the A-V conduction system. Of these 264 patients, 14 had complete block and of these one was 22 years old, 16 had a partial block and of these two were 24 and 29 years old, respectively. There were 23 other patients below the age of 30 with an A-V conduction time of 0.20 seconds, or more. Included in these last 23 patients were patients acutely ill with rheumatic fever and diphtheria, patients with rheumatic and luetic heart disease as well as patients with no definite heart disease. Delayed conduction time due to digitalis was not included in the series of 23 young patients, but was included in the total collection of 264 patients of all ages. It becomes apparent, therefore, that heart block in the young is not an extreme rarity but rather constitutes an important portion of the total incidence of heart block. Instances of heart block in children and young people are for the most part recorded in scattered and single reports. Archigène² collected 39 cases. This collection and those of Yater³ (30 cases of congenital heart

* Read before the Association of American Physicians, Washington, D. C., May 9, 1933. Received for publication June 7, 1933.

From the Department of Medicine, School of Medicine, Tulane University, and The Medical Service, Touro Infirmary.

block), Wood and Rogers ⁴ (six cases of congenital heart block), and the personal series of Sprague and White ⁵ (11 cases of juvenile block), are the most important. Their bibliographies serve as the chief guides to the literature.

The frequency with which heart block occurs in the young is not the only astonishing feature. Equally surprising is the lack of serious symptoms in many patients and the ability of these patients to carry on the most strenuous lives. In many of them the bradycardia was the only finding of note, and even this was discovered in some instances accidentally at routine examination. The patient of de Massary and Lian,⁶ who had had a bradycardia from his earliest years, engaged in the most violent sports (horse racing, fencing and automobile racing) and had never suffered the slightest inconvenience until his thirty-third year when he began to have syncopal attacks. Others have gone through operations and severe illnesses such as pneumonia and whooping cough, as well as the childhood exanthems. There are on record six well authenticated cases of young women with heart block who have gone through pregnancy and confinement without difficulty, and apparently without any subsequent damage.⁷ Stokes-Adams syndrome was present in only a minority of the 99 cases. Clerc⁸ estimated its incidence as 30 per cent in the series gathered by his pupil Archigene.² It did not seem to be more frequent in complete block than in partial block.

The prognosis is thus much less serious than would have been anticipated. In many, in fact in most, of the cases referred to in this collection of approximately 100 the block was permanent, and the block was known to exist through many years. It is to these lasting blocks that I desire to call your attention rather than to the evanescent blocks incident to infectious disease, though in passing it may be stated that these latter probably occur more frequently than is usually thought. The patient of de Massary and Lian⁶ to whom reference has already been made, had a bradycardia at birth. His syncope began and the heart block was proved when he was 34. He was still living 10 years later. The bradycardia of Calandrie's⁹ patient also dated from birth, the heart block was proved at the age of 21, when the patient still had no symptoms. Zander's¹⁰ child, who was seven in 1912 when the diagnosis was established, was seen again in 1925, 13 years later, when he had no complaint. Two cases are recorded in the literature, that are not included in the group of 99 but that are worth recording in this connection. Taussig's¹¹ patient of 70 knew, according to her family, that she had had since birth a slow pulse, accompanied by nervous crises. She had borne children. Jacquier's¹² patient of 78 had a slow pulse, noted in the first days of his life, remarked upon by his doctor at that time, and the bradycardia continued throughout his life. At 78 his pulse was 26 on awakening, 32 after he walked a few minutes, or climbed the stairs. He had never had syncope or vertigo. While it is true that absolute proof of heart block throughout these long lives is lacking, the presumptive evidence is extremely strong. Willius¹³ observed the course of his patient from 41 to 57 years

of age She had known of the bradycardia since the age of 36, and presumably it dated to diphtheria at 31 She had had no syncope nor any symptoms related to the heart Hyman's ¹⁴ patient, who was shown to have a complete block at 57, had known of his slow pulse since the age of 12, and could always get sick leave from school by having his pulse counted He had worked in all corners of the world under arduous physical and mental conditions At 57 he had no syncope, and his physical examination revealed nothing of importance other than heart block While in general, young patients with heart block often live normal lives, still it must be recorded that they are liable to sudden death Aldrich's ¹⁵ patient died on entering the water to swim, although she had previously swum frequently

We must, of course, in these young patients look for causes of heart block entirely different from those found in the aged, in the latter, arteriosclerosis, coronary disease, and myocardial fibrosis constitute the chief basis White ⁵ considers the following classes of heart block in the young from an etiological standpoint: (1) acute infections, (2) rheumatism, (3) congenital abnormalities, (4) trauma, and (5) idiopathic, he has himself reported examples from each class Of the acute infections he places diphtheria foremost, an opinion concurred in by Clerc ⁸ White ⁵ writes, however "When dissociation of the auricles and ventricles arises in the course of acute diphtheria, the patient is critically ill, and in the great majority of cases does not live long It still remains to be demonstrated conclusively that diphtheria is the agent responsible for heart block lasting more than a few days A study we have recently made of 100 patients following severe diphtheria, has revealed no persistent heart lesion" Butler and Levine,¹⁶ on the other hand, after studying a group of 20 patients with proved heart block without the customary causes, such as coronary heart disease, digitalis, fever, and rheumatic infections, and finding in 50 per cent a history of diphtheria in childhood, in contrast with a history of diphtheria in only 6 per cent of 600 consecutive controlled surgical cases, came to the conclusion that "diphtheria in childhood appears to be an etiological factor in the development of heart block in later years" At any rate diphtheria looms large in the histories, and in some cases a block dates back to the diphtheria ⁵ Various other infections have been incriminated because of the heart block developed in their course Influenza has been definitely so connected, as has typhoid Most important, of course, is the rôle played by rheumatism The block may be temporary or permanent

Heart block was congenital in 42 of the approximately 100 published cases This chapter of congenital heart block has in recent years dominated the picture of juvenile block in the literature Yater ³ in 1928 gathered 29 cases (some are included in Archigène's ² series), and added one of his own Wood and Rogers ⁴ in 1932 added six more cases from the literature with one of their own To this total of 37 I now add three more from the recent literature (Sprague and White,⁵ Švejcar and Francova-Helbichova,¹⁷ and Godfrey and Palmer,¹⁸ as well as two more from Archigène's series (de

Massary and Lian, and Calandre)), which seem to me to deserve to be considered congenital. This makes a total of 42 cases of congenital heart block.

Congenital heart block is apparently related to congenital anomalies for evidence was usually present in the reported cases warranting the diagnosis of these latter. Chief among these anomalies was the presence of a defect in the interventricular wall, giving rise to a loud systolic murmur heard over the whole precordium, to cyanosis and to club fingers. Carter and Howland¹⁹ have pointed out that an abnormal fetal development of the ventricular cavities and the interventricular septum may involve a group of cells later to become the A-V node and the upper part of the main stem of the conducting system. Indeed, as these authors state, in view of the definite relationship between the main trunk of the conduction system and the interventricular foramen, it is interesting that more frequent disturbance of the conduction system is not met with when anomalies of the septum are present. Unfortunately only four²⁰ autopsies have been reported on patients with congenital heart block. All of these showed septal defects. Other abnormalities suspected, but not proved, were aorto-pulmonary patency, pulmonary artery stenosis, and pulmonary valve stenosis. It has been suggested by Yater³ that prenatal endomyocarditis might be responsible for congenital heart block. The mother of the Wood and Rogers¹ patient had had rheumatic infection in her pregnancy. There is no evidence that antenatal syphilis plays a rôle. One of the children with heart block was found at autopsy to have a lymphangio-endothelioma of the A-V node.²¹

The following two cases illustrate in general the points already outlined. The first one possesses interest from a diagnostic and prognostic standpoint in certain particulars not hitherto stressed.

CASE I

A young man, aged 28, in vigorous health and of athletic type and habit, two hours after his usual horizontal bar exercise, September 19, 1930, developed a thumping in the heart region which had continued until he consulted me September 23. Shortly after the thumping began he developed a pain in the sternal region which continued during his waking hours until September 22, it was not agonizing but rather like a pressure. Neither the thumping nor the pain was aggravated by exercise and neither interfered with his sleep. When he awoke September 20 and 21 these symptoms reappeared. He continued with his work September 20, although whenever he got up he was dizzy. He still did not consider himself ill and drove his automobile for a week-end visit some forty miles on Saturday, September 20. On September 21, after he had retired he began to have cold sweats and waves of heat beginning at his legs and coming up over his body. He vomited after being given a purgative, and soon thereafter lost consciousness and apparently fell down trying to get out of bed. The noise of the fall brought his host into his room. The unconsciousness lasted five minutes. A doctor summoned found the pulse 24, and it remained 24-30 all day September 22. The patient drove himself back to town the morning of September 23, and at the time of his consultation (3 p.m.) felt as well as he ever did.

He had had measles, mumps, scarlet fever and pneumonia in childhood, denied having had malarialism or diphtheria. He had had no venereal disease.

The physical examination revealed nothing of importance. The heart rate was 72 and regular. There was no murmur. The blood pressure was 108/70. The fluoroscopic examination revealed a heart of normal size. The next few days he continued to have dizzy spells. On September 26 he was examined for life insurance by another doctor who found the heart rate 40. By the time the patient came to me, half an hour later, the heart rate was again 72. An electrocardiogram was made immediately and fortunately he was caught in a period of complete block. This electrocardiogram, September 26, 1930, showed an inconstant atrioventricular block (2:1 at times, at other times no block was present), P R, 0.28, when all auricular impulses passed to the ventricle, Q R S, 0.14 (intraventricular delay). R_1 , R_2 , R_3 slurred, left ventricular preponderance. He was given barium chloride $\frac{1}{2}$ grain three times a day from September 28. On October 3 the note was made that he had had no

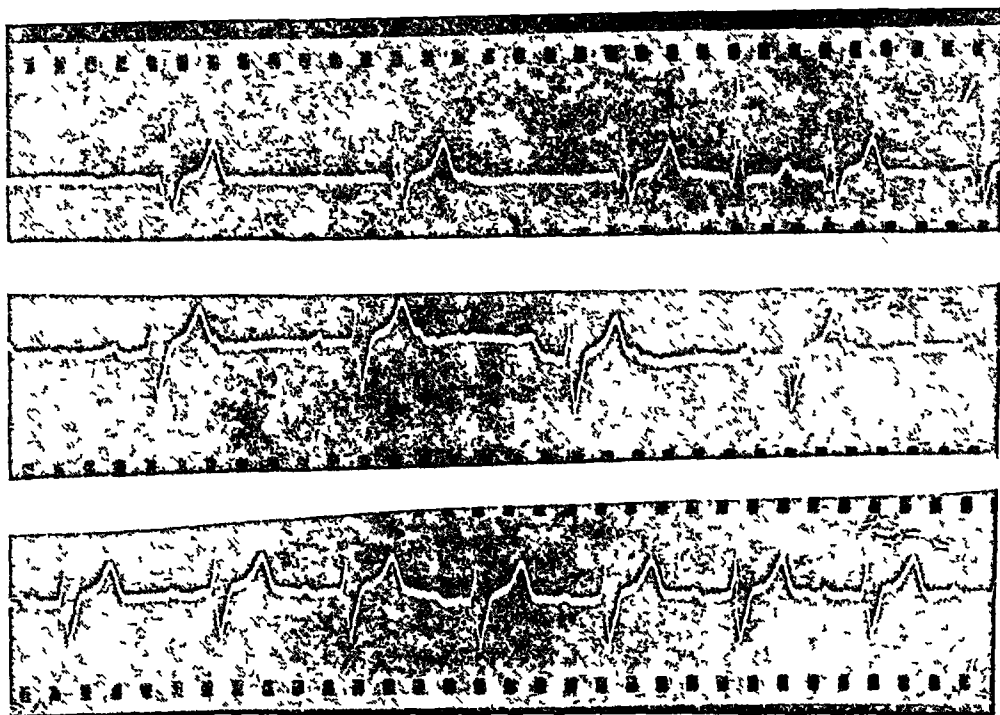


FIG 1 Case I (Age 28 9/26/30) Electrocardiogram Inconstant atrioventricular block (2:1 at times, at other times no block was present) P R, 0.28, when all auricular impulses passed to the ventricle Q R S, 0.14 (intraventricular delay) R_1 , R_2 , R_3 slurred Left ventricular preponderance

dizzy spells. A second electrocardiogram was made October 4. Sinus rhythm, auricular and ventricular rate, 60, P R, 0.16, Q R S, 0.12 (intraventricular delay), no atrioventricular block, R_1 , R_3 notched, R_2 slurred, T_2 inverted, right ventricular preponderance. The barium was discontinued after October 23. In June 1931 he reported that he had had for three or four weeks fleeting sensations of imminent fainting three or four times daily. At times also he had had sharp sudden pains near the upper part of the sternum, only for a minute which cut short his breath. At this time the heart and pulse were 72. When seen on March 28, 1933, he reported that he had not had the slightest indication of trouble, no dizziness ever, had been swimming without discomfort, during this winter he had paddled a pirogue three or four miles, and had hunted, walking knee deep in water and mud, all without trouble. He had been married 18 months. The physical examination showed nothing new heart, not

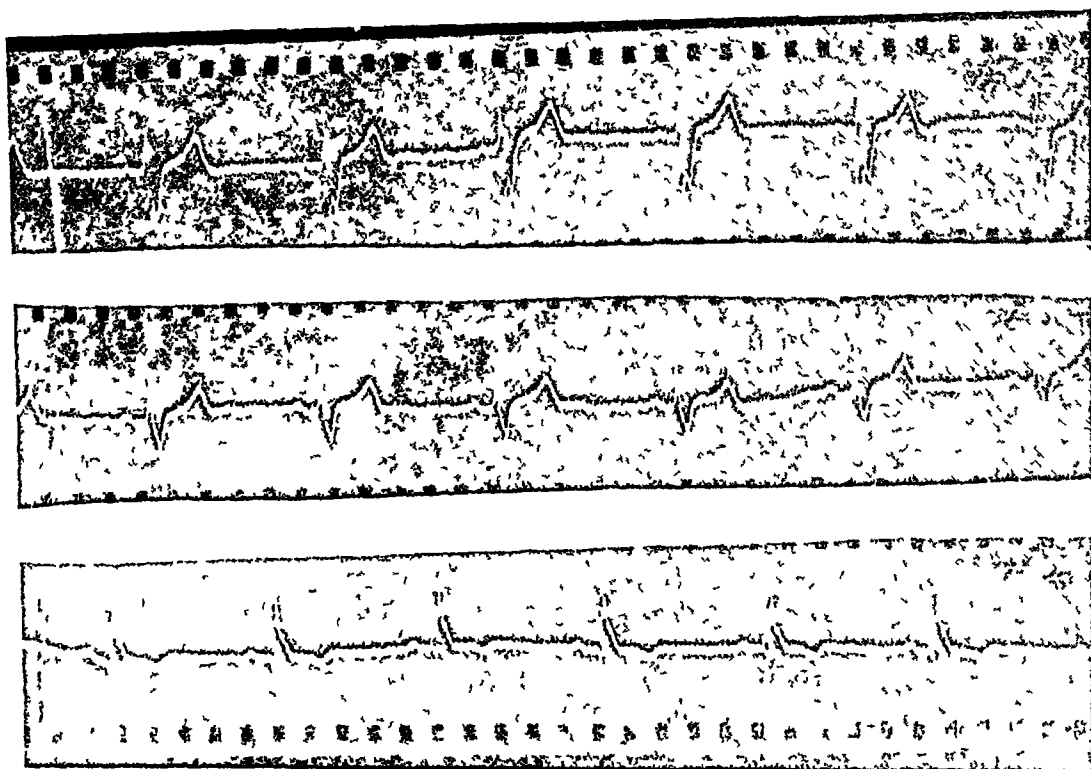


FIG. 2 Case I (Age 28 10/4/30) Electrocardiogram Sinus rhythm Auricular and ventricular rate 60 P-R, 0.16 Q-RS, 0.12 (intraventricular delay) No atrio-ventricular block R_1 , R_2 notched, R_3 slurred, T_3 inverted Right ventricular preponderance

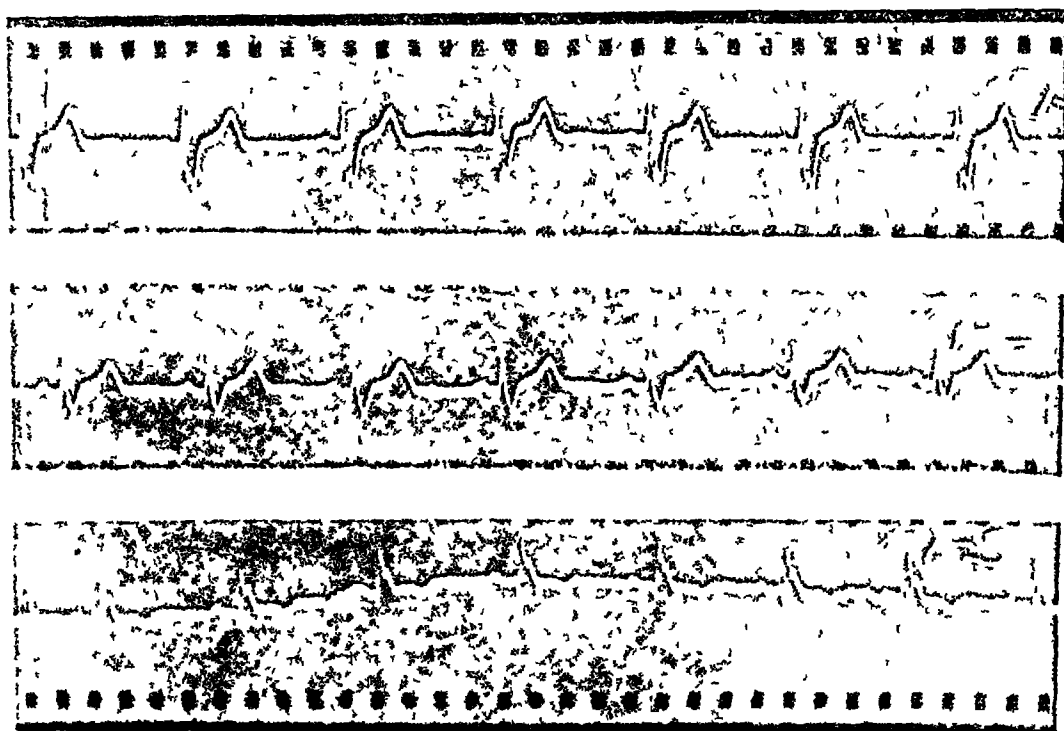


FIG. 3 Case I (Age 28 3/28/33) Electrocardiogram Auricular and ventricular rate 65 P-R, 0.16 Q-RS, 0.10 S_{1-3} notched, T_3 inverted, $S-T_{1-3}$ elevated Bundle branch block probably right

enlarged, no murmur. Blood pressure 116/82. Electrocardiogram auricular and ventricular rate 65, P R, 0 16 +, Q R S, 0 10, S_{1-2-3} notched, T_3 inverted, S-T₁₋₂ elevated, bundle branch block, probably right.

Here then is a heart block of unknown etiology, apparently coming on abruptly, giving rise to frequent Stokes-Adams attacks which were controlled by the administration of barium chloride and did not return after its cessation. Although the electrocardiogram continued to show, after two and one-half years, evidence of intraventricular conduction disturbance (bundle branch block) the patient suffered no inconvenience. This patient differs from others reported first in that the block was not constant, second that the Stokes-Adams symptoms were severe, and third that with the passing of the atrioventricular block there remained bundle branch block.

CASE II

A young woman 23 years old was brought to my attention by Dr W R Wirth. In 1928 she underwent a routine examination preparatory to entering gymnasium classes at the Y W C A. Her slow pulse was noted and she was advised to consult her family doctor. When I saw her in December 1932, she had been attending these

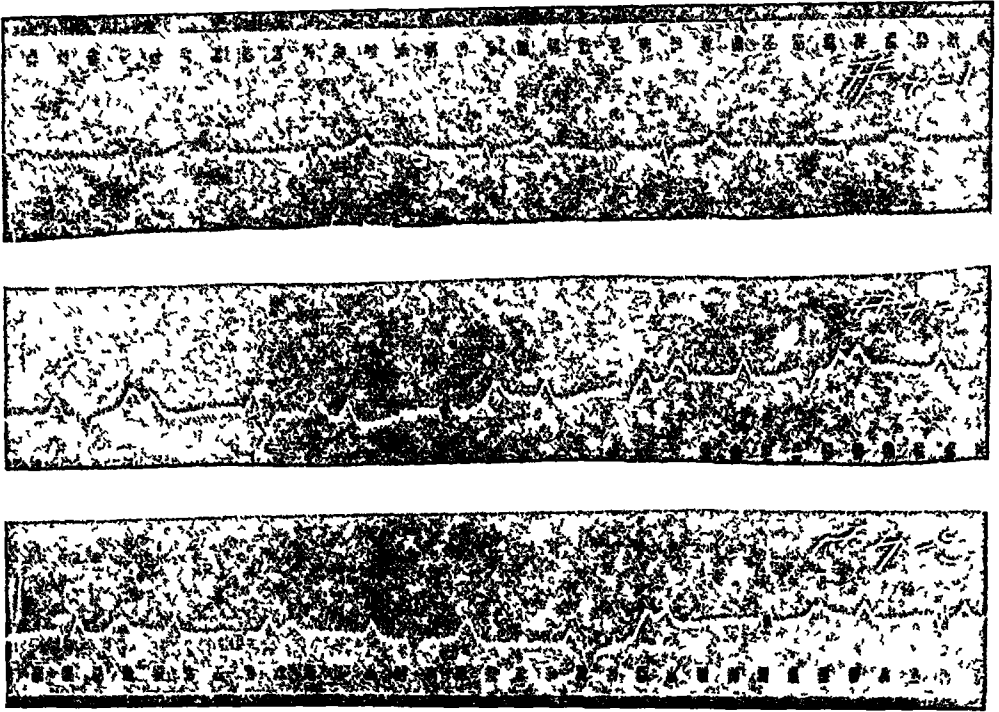


FIG 4 Case II (Age 23 12/5/32) Electrocardiogram Complete atrioventricular block Auricular rate 90 Ventricular rate 55 Q R S, 0 07 Right ventricular preponderance

classes for four years. They consisted chiefly of setting up exercises. She felt no bad effects, rather she usually felt better after them. Swimming 40 feet, however, caused marked dyspnea, and she also had some dyspnea after dancing or after running three blocks. She had never fainted, nor had any dizziness. There was nothing of interest in her past history. She had had measles and mumps as a child, she denied having had diphtheria or rheumatism. Tonsillectomy had been performed in September 1930 on account of occasional sore throat. She had had influenza in 1918 but it was not severe.

The physical examination revealed a young woman in apparent full health, and was negative except for heart findings. Heart and pulse rate were 50, and regular. There was a loud systolic murmur at the apex transmitted out to the left anterior axillary line. The same murmur was heard over the base and over the whole precordium. Blood pressure 120/60. Fluoroscopic examination, no enlargement of the heart. On one occasion, when the patient was made to hop 100 times, the heart rate did not increase (56 before, 58 after hopping). Slight dyspnea was noted after exercise. Electrocardiogram, complete atrioventricular block, auricular rate 90, ventricular rate 55, Q R S, 0 07, right ventricular preponderance.

This patient with a heart block of unknown origin has suffered little or no inconvenience in the four years that it has been recognized or suspected. In the absence of any history of diphtheria or rheumatism, we must attribute it to the influenza in 1918, or to the frequent sore throat. The murmur represents, in all probability, the endocardial damage done by the same factor. We find no basis in the history, or in the physical examination, for assuming that the block is congenital, or due to septal anomaly.

CASE III

This case was brought to my attention by Dr. Maurice Sullivan. A young man, aged 32, without complaint was sent home from one of the Civilian Reforestation Camps because of a bradycardia discovered at routine physical examination. Our physical examination showed the apex beat just beyond the left nipple line and a systolic murmur at the apex. The electrocardiogram revealed a complete atrioventricular block, the auricular rate being 65, the ventricular 42. The patient denied ever having been ill except for influenza in 1918.

CASE IV

A young woman aged 31, in apparently perfect health, had two attacks of syncope in which the heart rate was counted by competent physicians as 30. An electrocardiogram taken in an interval failed, however, to show any disturbance of rhythm or conduction. We can, therefore, only surmise that we were dealing with a transitory block.

SUMMARY

A review of the literature shows that heart block in the young is by no means a rare condition. Of approximately 100 cases, about 42 per cent are congenital and associated with a developmental deformity. Diphtheria, rheumatism and influenza are important etiological factors. There is reason to believe that heart block in hearts not the site of degenerative changes is not incompatible with long life. Many patients have no Stokes-Adams attacks and suffer no inconvenience. On the other hand, the possibility of its existence should be considered when we are dealing with fainting spells and convulsive movements in the young.

REFERENCES

1. WHITE, P. Heart disease, 1931, Macmillan Company, New York, p. 673.
2. ACHILLE, J. D. Thèse de Paris, 1927.
3. YARF, W. M. Congenital heart block, review of literature, report of case with incomplete heterotaxy, electrocardiogram in dextrocardia, *Am. Jr. Dis. Child.*, 1929, xxxviii, 112-136.

- 4 WOOD, W A, and ROGERS, H Congenital heart block, report of case, Calif and West Med, 1932, *xcvi*, 397-398
- 5 SPRAGUE, H B, and WHITE, P D High-grade heart block under age of thirty, Med Clin North Am, 1927, *x*, 1235-1250
- 6 DE MASSARY and LIAN Quoted by Archigène²
- 7 JEANNIN, C, and CLERC, A Dissociation auriculo-ventriculaire et grossesse, Bull et mém Soc med d hôp de Paris, 1927, *li*, 122-127
CLERC, A, and LEVY, R Evolution de la dissociation auriculo-ventriculaire chez les jeunes sujets, Bull et mém Soc med d hôp de Paris, 1928, *lii*, 490-498
LAUDRY Quoted by Archigène²
- TITUS, R S, and STEVENS, W B Normal pregnancy in patient with preëxisting complete heart block, Am Jr Obst and Gynec, 1931, *xxii*, 773-777
- DRESSLER, W Schwangerschaft und Herzblock, Wien Arch f inn Med, 1927, *xiv*, 83-96
- HERRMANN, G, and KING, E L Cardiovascular disturbances in the obstetric patient, Jr Am Med Assoc, 1930, *xcv*, 1472-1476
- 8 CLERC, A, and LEVY, R Evolution de la dissociation auriculo-ventriculaire chez les jeunes sujets, Bull et mém Soc med d hôp de Paris, 1928, *lii*, 490-498
- 9 CALANDRE Quoted by Archigène²
- 10 ZANDER Quoted by CLERC and LEVY⁸
- 11 TALSSIG Quoted by Archigène²
- 12 JACQUIER Quoted by Archigène²
- 13 WILLIUS, F A Complete heart block of unusually long duration, Proc Staff Meet, Mayo Clinic, 1931, *vi*, 196-200
- 14 HYMAN, H T Asymptomatic heart block of long duration, Jr Am Med Assoc, 1930, *xciv*, 27
- 15 ALDRICH Quoted by LAMPARD, M E Heart block associated with congenital heart disease, Arch Dis Childhood, 1928, *iii*, 212-220
- 16 BUTLER, S, and LEVINE, S A Diphtheria as cause of late heart block, Am Heart Jr, 1930, *v*, 592-598
- 17 ŠVEJCAR and FRANCOVÁ-HELBICHOVÁ, A Rare case of congenital cardiopathy associated with sino-auricular block in infant, Časop lek česk, 1931, *lxx*, 1775-1777
- 18 GODFREY, J W, and PALMER, R S Congenital complete heart block, report of additional case, New Eng Jr Med, 1932, *ccvii*, 575-577
- 19 CARTER, E P, and HOWLAND, J Occurrence of congenital atrio-ventricular dissociation, report of case of congenital complete heart block, Bull Johns Hopkins Hosp, 1920, *xxvi*, 351
- 20 WILSON, J G, and GRANT, R T A case of congenital malformation of the heart in an infant associated with partial heart block, Heart, 1925, *xii*, 295-305
YATER, W M Congenital heart block, report of case with incomplete heterotaxy, Proc Staff Meet, Mayo Clinic, 1928, *iii*, 320-322
ABBOTT Personal communication to WHITE Quoted by GODFREY and PALMER¹⁸
PEROTTI Quoted by YATER³
- 21 ARMSTRONG, H, and MONCKEBERG, J G Herzblock, bedingt durch primären Herztumor, bei einem 5-jährigen Kind, Deutsch Arch f klin Med, 1911, *cii*, 144-166

EDITORIAL

AMEBIASIS

THE REPORTS in the press of an outbreak of amebic dysentery in Chicago, which has apparently been traced to infected food handlers, should draw the attention of the medical profession to what Craig¹ has called "the amebiasis problem"

Though amebic dysentery and its most frequent complication, hepatic abscess, are seen with relative frequency in the southern states and are not rare in the northern part of this country, it is not in connection with these outspoken clinical manifestations of amebiasis that the main problem exists; it is rather with the far greater number of instances in which amebiasis is present without producing any characteristic symptoms. The stools of these latent cases of amebiasis are more apt to contain the *Endameba histolytica* in its encysted than in its vegetative form, and since it is the amebic cyst which serves to transmit the disease, each latent case is a potential source of danger to others. The disease which is latent in the "carrier" may, when transmitted to another, assume a virulent dysenteric form. Human "carriers" are believed to constitute the chief source from which, by transmission of infected fecal material, arise the acute cases of amebic dysentery in this country. The rôle of certain animals, rats, pigs and dogs, which have been shown to be occasional carriers, is probably a relatively minor one. The amebic cysts in human or animal feces are sufficiently resistant to remain viable for a number of days, or even weeks in a moist medium.² Flies may carry such infected fecal material in their digestive canals and deposit amebic cysts in their feces on human food. Water supplies may become infected and serve as a medium for the transmission of the cysts. More usually it is the hands of the "carrier" which become contaminated and inoculate the food supply of others. The carrier who is also a food handler is the chief source of danger. A survey in Chicago in 1927 showed that 2.35 per cent of the 1148 food handlers examined were carriers of the *Endameba histolytica*.³

An even more important aspect of the problem of latent amebiasis is the possible effect of the chronic subclinical infection on the carrier himself. The number of cases of amebic dysentery and of amebic abscess that occur in this country yearly cannot be exactly stated, but to judge by the reported cases this number would not exceed a few thousand. The results of surveys by competent authorities would indicate, however, that the cases of latent amebiasis in the United States must be numbered in the millions.

¹ Craig, C. I. The amebiasis problem, Jr. Am. Med. Assoc., 1932, xxviii, 1615-1620.

² Wright, F., and Wright, V. On the viability of cysts of *Endameba histolytica* under artificial conditions, Am. Jr. Trop. Med. 1932, xii, 381-387.

³ Whitman, C. S., Kania, B., and Greiner, J. C. A survey of amebic dysentery in Chicago, Jr. Am. Med. Assoc., 1929, xii, 528.

Craig,¹ in 1932, after a review of these surveys, concluded that "enough has been done to warrant the statement that it is conservative to estimate that between 5 and 10 per cent of the people of this country harbor *Endameba histolytica*"

The results of these surveys have been discounted by some on the assumption that there must exist avirulent strains of endameba not readily distinguishable from the *Endameba histolytica*. Brumpt has described such avirulent species. His work, however, lacks confirmation and is contradicted by the mass of experimental work showing that the cysts from cases of asymptomatic amebiasis are pathogenic to animals and, as Walker and Sellards showed, also to man. A more difficult question to answer is whether latent amebiasis in humans is always accompanied by pathological lesions. Evidence to the contrary is not available, but neither is there on record a sufficient number of autopsy studies on cases of latent amebiasis to yield conviction that lesions in the intestines of such cases are always present. The most important contribution in this field is that of Bartlett,⁴ from Egypt, during the World War. He described the postmortem findings in 11 cases which had never in life presented symptoms of diarrhea or dysentery but had shown *Endameba histolytica* in their stools. All were found to show amebic ulcerations, in some instances extensive, in their colons. Sufficient scattered similar cases are on record to show conclusively that very definite lesions may exist without sufficient symptoms to attract attention. It is believed by some that a constant process of formation and healing of small ulcers probably goes on in the large bowel of these asymptomatic cases. On the other hand, Andrews and Atchley⁵ found little evidence of occult blood in the feces of carriers of *Endameba histolytica*. From animal experiments it would seem that the endameba cannot persist in the lumen of the bowel without attacking the mucosa. In view of the importance of the question, it is highly desirable that further investigations should be carried out.

A conservative position must likewise be taken as to the question of constitutional symptoms due to latent amebiasis. It is certain that many cases are entirely asymptomatic. It is probable, however, that in certain instances vague digestive discomforts, neuralgias and general asthenia, may be caused by the otherwise latent amebic infection.

In view of the constant advances that have been made in the therapy of amebiasis, it is perhaps reasonable to believe that a safe, efficient, and not too expensive remedy may be available with which to attack the problem offered by the truly appalling number of latent cases of this disease.

It is apparent, however, that no program can, nor perhaps should be formulated, until further data have been accumulated bearing on the pathology and the constitutional effects in humans of latent amebiasis. The collection of such data is almost entirely dependent upon an awakening of

⁴ BARTLETT, C. Quart. Jr. Med., 1917, x, 185. Quoted by CRAIG, C. F. Pathology of amebiasis in carriers, Am. Jr. Trop. Med., 1932, xii, 285-299.

⁵ ANDREWS, J. and ATCHLEY, F. Negative occult blood tests in carriers of dysentery-producing *Endameba histolytica*, Jr. Am. Med. Assoc., 1932, xcix, 1340-1342.

interest among physicians as to the practical importance of this whole question. So far, we owe our knowledge of the subject largely to the devoted labors of a relatively few men many of whom are primarily parasitologists. The clinician has the opportunity to make important further contributions.

The average hospital has lagged far behind present day methods in the diagnosis of amebiasis. Parasitology is in general the weakest department in most clinical laboratories. The examination of the stool is usually the most perfunctorily carried out of all laboratory procedures. Dougherty⁶ reports results obtained from the records of the larger hospitals in 13 southern cities between 1927 and 1931. "*Endameba histolytica* was demonstrated in the stools of 396 cases reported, and out of this number 336 were in hospitals with complaints directly referable to acute or chronic amebic dysentery or abscess of the liver." One must deduce that in five years in the larger hospitals of 13 cities only 60 cases of latent amebiasis were discovered. During this same period in 1930 Faust⁷ conducted a survey of the patients in the Charité Hospital in New Orleans. He found 27.2 per cent of infections with the endameba in the male medical wards, 13.1 per cent in patients in the female medical wards, 25.2 per cent in the obstetrical wards and 8.27 per cent in medical students. His single survey of only 1100 individuals disclosed 150 cases of amebiasis. The failure of our present routine diagnostic measures in general hospitals can scarcely be more strikingly demonstrated. It is probable that the more general adoption of cultural methods for the ameba would result in an awakening of fresh interest in the diagnosis of amebiasis. The preparation of the medium has of late been much simplified. The growth contains the protozoa in the vegetative form and in relative abundance, especially in subculture. The time involved is probably no greater than what is required for adequate examination of fresh specimens and less than that demanded by the preparation and study of hematoxylin stained smears. Moreover the cultural method in many hands (Stitt,⁸ Craig, Spector⁹) yields a higher percentage of positives than study of smears. Finally, the stimulus of definite diagnostic findings might awaken physicians and clinical pathologists to a more careful consideration of the clinical aspects of these latent forms of amebic infection.

⁶ DOUGHERTY, M. S., JR. Amebiasis, a public health problem in the cities of the southern United States, *Am. Jr. Trop. Med.*, 1933, **xiii**, 317-327.

⁷ FAUST, E. C. The incidence and significance of infestation with *Endameba histolytica* in New Orleans and the American tropics, *Am. Jr. Trop. Med.*, 1931, **xi**, 231.

⁸ STITT, E. R. The diagnostics and treatment of tropical diseases, 5th Edition, 1929, P. Blakiston Sons and Co., Philadelphia, p. 193.

⁹ SPECTOR, B. K. A comparative study of cultural and immunological methods of diagnosing infections with *Endameba histolytica*, *Jr. Prev. Med.*, 1932, **vi**, 117-128.

REVIEWS

Life in the Making By ALAN FRANK GUTTMACHER, Associate in Obstetrics, Johns Hopkins University, with the assistance of ELLERY RAND 297 pages The Viking Press, New York 1933 Price, \$2.75

The author, in a free-flowing and interesting style, has recorded the story of the development of our present knowledge of sex. He has brought into a logical sequence facts that to most of us were uncorrelated bits of sex knowledge. In so doing he has drawn upon a wide knowledge of very diverse realms of scientific literature, and has given to his book real value as a reference volume.

The book is divided into six parts. The first deals with the numerous misconceptions that have arisen during the ages concerning the way in which life begins and ends, with a detailed account of our present knowledge of the sperm and egg. The second part deals with different types of sex behavior. Here the author does not limit himself to man but records many of the observations that have been made of the sex life of animals. This portion of the book will be of as much interest to the biologist as to the physician. Indeed, the reviewer, who happens to be a physician, believes he found this section interested him more than did any other part of the whole book. Another section points out that in spite of the numerous advances that have been made in sex knowledge, man is today still as unable to control sex or even to determine sex before birth as he ever was. The last section of this book deals with twins, and because the author himself is an identical twin the records of his personal feelings on this matter have a special appeal.

Nurses, physicians, and biologists will find this book of great interest, but possibly the average adult layman, for whom the book has been especially written, will be disappointed. The rather startling outer cover will be likely to attract the layman, but the very complete historical sketches, combined with the great number of scientific facts, may overwhelm him and cause him to lose interest. These same features are the elements that make Dr. Guttmacher's work of great value to all those really interested in biological and medical problems, and of particular interest to those who specialize in obstetrics and gynaecology.

L. B.

Osteitis Deformans A Review of the Literature and Report of Eleven Cases Public Health Service Bulletin No 209 By J. W. KERR, Medical Director, United States Public Health Service Washington Government Printing Office 1933 Price, 10 cents

This Bulletin, comprising 122 pages with bibliography, contains a review of reports appearing in the literature during the period 1876 to 1928 and also reports upon 11 additional cases from among beneficiaries of the Public Health Service. The analysis is approached from the standpoint of the history of the disease, its geographical distribution, and the occurrence of similar disease in animals. Its frequency in man, hereditary factors, race, sex, color, occupation, mental status, environment, habits, and mental attitude of patients are considered. General symptomatology, order of involvement of bones, other features such as the appearance of syphilis and malignancy, and associated disorders of the vascular and genito-urinary system, blood, skin and its appendages, eye, ear, neurological and psychiatric components are discussed. The chemistry, changes in ductless glands, and other pathological bone changes are referred to. Salient points in diagnosis are outlined and past views on treatment recorded.

The outstanding features of the disease as reported appear to be a greater prevalence in cold climates, hereditary factors, lack of association with syphilis, its liability to affect the special senses, and sarcomatous formation. From a pathological standpoint, the author considers the disease closely related to osteomalacia and possibly identical with osteitis fibrosa and leontiasis ossea. Because of their similarity in pathology during some stage of the disease, the author suspects that all may be due to the same underlying cause. He says "Its etiology is unknown. Discovery of the cause will probably throw light on this whole group of diseases. Every effort should be made to detect cases and record the results. Systematic research should be conducted to clarify the etiology and abnormal metabolism. The bearing of heredity, the functions of the internal secretions, the newer views regarding nutrition and the tendency to malignancy should all be taken into account in attempts to throw light on the underlying cause of the affection."

W L T

Psychoanalysis and Medicine: A Study of the Wish to Fall Ill. By KARIN STEPHEN, M A, M R C S, L R C P, Sometime Fellow of Newnham College, Cambridge. 238 pages. The MacMillan Company, New York. 1933. Price, \$2.50.

Dr Ernest Jones, in a short preface to this book, states "It would be hard to think of a better introduction to this complex study, than that which her book offers." With this statement, we heartily agree. Written in a clear, logical manner, it is free from the exaggerations that so frequently mar books on the subject of psychoanalysis. The average physician may not agree with many of the concepts here elucidated, but he will nevertheless find much that is helpful in understanding the chronic invalid. Although of chief value as an aid in dealing with psychoneurotic conditions, it should be of help in understanding the mental phases of organic disease.

A C G

History of Urology. Volumes I and II. Editorial Committee: BRANSFORD LEWIS, Chairman, EDGAR G. BALLINGER, WILLIAM A. FRONTZ, and HOMER G. HAMER. xi + 385, 17 x 24 cm. Williams and Wilkins, Baltimore. 1933. Price, \$8.00 for 2 volumes.

This two-volume work on the history of urology was prepared under the auspices of the American Urological Association, and has been written by the editorial committee composed of Drs. Bransford Lewis, Edgar G. Ballinger, Homer G. Hamer, and William A. Frontz, together with 26 other collaborators.

While it is a general history of urology and depicts in a very interesting way the knowledge of this specialty back to early historic times, the greater bulk of the work is, nevertheless, devoted to a more detailed exposition of the history of urology in the United States. Special sections are given over to the description of the development of urology in certain selected American medical centers. In addition to this geographic method of presenting material, there are separate chapters on special topics, such as, "Tests and Chemicals," "Diagnosis in Urology," "Focal Infections," and "Bacteriology." For the most part the book is very readable, even for those whose main interests are not in this field. It is always interesting, and in some sections it is distinctly amusing.

The striking advances made in this specialty and the great reduction in operative mortality in the surgical procedures are forcibly presented. These volumes constitute a noteworthy contribution to the history of modern medicine. They will interest not only urologists but all physicians who wish to obtain a sound perspective in considering the value of specialization or who desire to acquaint themselves with the status of modern urology.

M C P

To Be or Not to Be A Study of Suicide By LOUIS I DUBLIN, Ph D, and BESSIE BUNZEL, M A Harrison Smith and Robert Haas, New York 1933

The statistical method has been the chief tool at the disposal of the authors for a study of suicide They have brought together the main facts on the subject, pointing out, however, that there are many aspects of the problem and that it is not possible to cover all of them in a small volume They have compiled data on the frequency of suicide among various groups, on the changing rates from year to year, on the age, sex, and racial factors, on urban and rural incidence, together with methods used by those taking their own lives Factual material derived from older historical, philosophical and religious sources are presented, with a compilation of the scattered findings of other investigators

The book touches upon suicide among primitive people, upon the teachings, religious and ethical, which tend to encourage or prohibit, upon the prevailing sentiments and customs being crystallized in law, and upon causes and prevention Hardships of various kinds, including ill health, mental abnormality, physical pain, deformity, loss of honor, position, freedom, and love are all mentioned as objective causes But aside from this, the authors point out that there is the more important factor of the serious emotional maladjustments and conflicts that underlie attempts at suicide These individual emotional conflicts which often lead to suicide are in other instances modified, sublimated, or given a conventional solution in accordance with public opinion

The authors regard prevention of suicide as involving an understanding and an appreciation of the individual motives and emotional conflicts lying behind such attempts They review some of the mental mechanisms prompting such acts and describe plans already in operation for the prevention of suicide

W L T

The Adolescent Boy By WINIFRED V RICHMOND, Ph D, Psychologist, George Washington University, and St Elizabeth's Hospital, Washington, D C 233 pages Farrar and Rinehart, New York 1933 Price, \$2 50

Adolescence Studies in Mental Hygiene By FRANKWOOD E WILLIAMS, M D, former Medical Director, National Committee for Mental Hygiene 279 pages Farrar and Rinehart 1930 Price, \$2 50

Physicians are frequently faced with the necessity of counselling parents and their adolescent patients during the "crisis of life" Not all physicians have had the good fortune in their medical school days to have a series of lectures on the psychology of childhood, nor have they been able to complete a course of instruction in a child guidance clinic These two books which, since they deal with different aspects of this subject, are here reviewed together, constitute an excellent symposium on the problems of adolescent adjustment

Dr Williams' book, which has gone through three large printings, is a collection of eleven of his previously published essays It is a volume which will appeal to the sophisticated reader, inciting critical thought and challenging clearer thinking On the other hand, it will give very little solace to the troubled parent

The book is readable and lends itself well to quotation Something of its quality and the author's point of view may be gained from some excerpts "Mental Hygiene, like medicine, is an art not a science Ability to work in the field of mental hygiene is not a matter of good will or good intentions It is a matter of knowledge It is a field for the expertly trained At present the field is one for cooperative effort on the part of the psychiatrists, psychologists, educators and social workers, and success comes from a pooling of effort" "We try to force upon youngsters very unhealthy ideals Nobody knows as does the psychiatrist how devastating the damage has been to thousands of men and women through these unhealthy ideas"

"Parenthood is the only profession that can be practiced in America without definite instruction and preparation Any one may become a parent One learns therefore

on the job while occupied at the same time with many other time-consuming and energy-consuming jobs. There is no more inadequate method of learning than this nor one more wasteful of material. It is not surprising, therefore, that out of this situation come emotionally warped and misshapen personalities, some who protest vigorously—through their delinquency—others who become overpowered and tend to give up the conflict or to minimize it by retiring emotionally within themselves, a more agreeable type of child but probably a less healthy type than the former."

Dr. Richmond first wrote a book on the "Adolescent Girl," and apparently its success has led to the production of this very easily read and logically constructed book of eight chapters on the "opposite sex." It begins with a survey of the anthropological and historical background against which our modern youth must play his part, then logically takes up the problems of puberty with its deficiencies and abnormalities. As crime in recent years has become a very definite problem of adolescence, there is a discussion of the delinquent boy, but fortunately more than half of the balance of the book is devoted to the normal adolescent. It concludes with a discussion of "The Boy at College" and "The Young Man and the Changing World." The author reminds us that "in the light of our present knowledge we can review the mistakes of their up-bringing, can wish that we had been less arrogant, less short-sighted, less occupied with material things, and more interested in the intangible values of life. We have not given them the full measure of our confidence and understanding and even what we might have given them in preparation for the hardships they must undertake."

J. L. McC

Mental Deficiency Due to Birth Injuries. By EDGAR H. DOLL, Ph.D., WINTHROP M. PHELPS, M.D., and RUTH T. MELCHER, M.A., Training School at Vineland, N. J. 275 pages. Macmillan Company, New York. 1932. Price, \$4.50.

This book represents a very thorough study of birth injuries in the leading institution of this country for the care of mentally defective individuals. It is a timely report because of the ever apparent results of poorly handled obstetrical cases. As is pointed out in the preface: "The limitations of professional information and skill

render both diagnosis and treatment experimental, no matter from what angle the patient was considered. The best medical judgments describe the condition as Little's Disease, and offered no hope of amelioration."

This book thoroughly reviews the literature on the subject of birth accidents and analyzes the diagnosis of these neurologically handicapped patients. The book is fully illustrated and takes up the case histories of twelve such cases. A full bibliography, also, is given.

There is a great deal of misunderstanding in the medical profession on the matter of mental ability as measured through its functional expressions, language or movement. Unfortunately, the average practitioner does not realize that standards of normal mental development are built upon observation of total responses of mentally and physically average children in given situations. When a person is so seriously limited in motor activity as to interfere with his ability to express himself either through language or manipulation or both, we cannot directly compare his responses to test situations with those of the average child. Fortunately, this book fully discusses this question and helps to evaluate mental testing of neurologically injured persons.

Perhaps the most interesting and most valuable part of the book is the chapter on Physical Therapy which takes up the training of these unfortunates and gives a ray of hope to the obstetrician who has officiated at bringing into the world a child who apparently is doomed to a life of hopelessness.

The reviewer feels that this book is well worth the time it takes to read it, and that it will stimulate further research in this very important subject.

J. L. McC

COLLEGE NEWS NOTES

Acknowledgment is made of the following gifts of publications to the Library by members of the College

Dr Milton A Bridges (Fellow), New York, N Y—one book, "Dietetics for the Clinician",

Dr H Sheridan Baketel (Fellow), Jersey City, N J—one reprint,

Dr Oscar W Bethea (Fellow), New Orleans, La—five reprints,

Dr Hyman I Goldstein (Associate), Camden N J—one reprint,

Dr Ronald L Hamilton (Fellow), Sayre, Pa—two reprints,

Dr George H Hoxie (Fellow), Kansas City, Mo—two reprints,

Dr Oliver T Osborne (Fellow), New Haven, Conn—two reprints,

Dr Frederick R Taylor (Fellow), High Point, N C—one reprint,

Dr John Russell Twiss (Fellow), New York, N Y—three reprints,

Dr Joseph B Wolffe (Associate), Philadelphia, Pa—one reprint

Dr William R Brooksher (Fellow), Fort Smith, Ark, was elected Secretary-Treasurer of the Arkansas Medical Society at a meeting of its Council in Little Rock, September 15

Under the Presidency of Dr Joseph Yampolsky (Fellow), Atlanta, Ga, the first annual scientific meeting of the Georgia Pediatric Society was held in Atlanta, October 12

Dr Horton Casparis (Fellow), Nashville, Tenn, was one of the guest speakers, his subject being "Allergy in Children"

Dr Janvier W Lindsay (Fellow), Washington, D C, has been named to serve for a term of three years as Chairman of a Committee appointed by the President of the Medical Society of the District of Columbia to supervise a tumor registry established recently by the Society

Dr Walter J Freeman (Fellow) and Dr Matthew White Perry (Fellow), both of Washington, D C, were also appointed members of the Committee to serve for terms of three years each

Dr Waller S Leathers (Fellow), Nashville, Tenn, was elected Chairman of the newly created Public Health Council at its first meeting in Nashville during September

Dr Albert F Tyler (Fellow), Omaha, Nebr, was installed as President of the American Congress on Physical Therapy at its last annual meeting

Dr John S Hibben (Associate), Pasadena Calif, was elected one of the Vice-Presidents

The Radiological Society of North America, the American Roentgen-Ray Society, the American Radium Society and the American College of Radiology com-

bined their meetings under the title of the American Congress on Radiology at Chicago, September 25-30

Dr John T Murphy (Fellow), Toledo, Ohio, and Dr George W Grier (Fellow), Pittsburgh, Pa, were elected President and President-Elect, respectively, of the American Roentgen-Ray Society

Dr Rollin H Stevens (Fellow), Detroit, was elected President of the American Radium Society

Dr Thomas A Groover (Fellow), Washington D C, and Dr Benjamin H Orndoff (Fellow), Chicago, were elected President-Elect and Secretary, respectively, of the American College of Radiology

Dr Harlow Brooks (Fellow), New York City, and Dr Elliott P Joslin (Fellow), Boston, were guest speakers at the fourth annual fall Clinical Conference sponsored by the Oklahoma Clinical Society, October 30 to November 2

The following changes were made in a recent reorganization of the clinical departments of the College of Medical Evangelists, Los Angeles Those reported refer only to members of the College

Dr Charles C Browning (Fellow), Emeritus Professor of Tuberculosis,
 Dr John V Barrow (Fellow), Director of Clinical Teaching in the Department of Medicine, Los Angeles County General Hospital,
 Dr Carl R Howson (Fellow), promoted to Professor and Head of the Department of Tuberculosis,
 Dr Ben E Grant, Jr (Fellow), Associate Professor of Medicine

Dr Allen K Krause (Fellow), Tucson, Ariz, Dr Leonard G Rowntree (Fellow), Philadelphia, Pa, and Dr John H Musser (Fellow), New Orleans, La, were among the guest speakers delivering lectures at the second Post Graduate Medical Assembly of South Texas at Houston, November 21 to 24

Dr Louis Faugeres Bishop, Jr (Fellow), of New York, was appointed to the faculty of postgraduate medical study, University of Oklahoma, School of Medicine, for a circuit course October 9 to 13, Management of Coronary Artery Disease

A CENTRAL MALARIA LIBRARY

A malaria library was founded in Rome by the Stazione Sperimentale per la Lotta Antimalarica in 1925, and an "Index to Malaria Literature" is issued annually by the Station

To make this as complete a central malaria library as possible, the Director of the Library appeals to all malarialogists to send books and reprints of articles on malaria Photostat copies of many articles in the library can be had on request, at cost of production

All publications and requests should be addressed to The Director, Stazione Sperimentale per la Lotta Antimalarica, Corso Vittorio Emanuele 168, Rome (16)

OBITUARIES

DR SAMUEL FRANKLIN ADAMS

Samuel Franklin Adams, M D , M S in Medicine (University of Minnesota), F A C P , died suddenly, September 28, while traveling by ambulance from his home in White Plains, New York, to the Grasslands Hospital, Valhalla, New York. He was suffering from pneumonia of only twenty-four hours' duration, and it was not suspected that any condition existed which might prove fatal.

Dr Adams was born in Jersey City, New Jersey, July 27, 1896. He attended Dickinson High School, Jersey City, the University of Pennsylvania 1914-1915, and Wesleyan University, Middletown, Connecticut, 1915-1916. In 1916 he entered New York Homeopathic Hospital and Flower Hospital from which he was graduated in 1920. After a year's internship in Buffalo Homeopathic Hospital and three months of practice in Jersey City, he entered The Mayo Foundation September 28, 1921, as a fellow in medicine. In 1922, he was appointed first assistant in a section on medicine of The Mayo Clinic, associate in 1925, and in 1927 instructor in medicine, The Mayo Foundation, Graduate School, University of Minnesota. He was made a Fellow of the American College of Physicians in 1926.

In 1931, Dr Adams left The Mayo Clinic to enter practice in New York City. At the time of his death he was assistant professor of medicine at his alma mater, on the staffs of the Flower Hospital and the Metropolitan Hospital, New York, and of St Agnes' Hospital, White Plains, and White Plains Hospital. He was also on the staff of Grasslands Hospital, Valhalla, New York, where he had organized a metabolic clinic of which he was the head. He was a Fellow of the American Medical Association, a member of Sigma Xi, and a member of the Central Society for Clinical Research.

A record such as this needs little amplification, but there are matters, fully as important, concerning which a bare list of achievements is silent. Dr Adams' too short medical career almost corresponded with the first ten years of insulin treatment of diabetes, and of the twenty some medical papers which bear his name, three-fourths are on the subject of diabetes. His field of second interest was disease of the blood vessels, in which, as in other branches of medicine, he was recognized as a brilliant student and internist.

With all of his ability in his work, Dr Adams was nothing of the grind. Apparently, mastery of difficult subjects came to him without effort. And so it was with his avocations. His wit, energy and broad reading, and his ability in music and in sports made him the center of any gathering in which he found himself. At various times and in various social or semi-professional organizations Dr Adams was elected to the presidency or to

some other office of responsibility, the duties of which he discharged with universal satisfaction

In 1920, Dr Adams married Miss Ethel S Greene who, with three children, survives him

GEORGE E BROWN, M D , F A C P ,
Rochester, Minn

DR WILLIAM RAY BATHURST

Death removed one of the outstanding members of the Arkansas medical profession when Dr William Ray Bathurst died suddenly August 31, 1933, at the age of 57

A native of Pennsylvania, most of his professional career was spent in Arkansas where he had served well both his patients and his associates. Following his graduation from the Medical Department of the University of South in 1899, Dr Bathurst studied at the Philadelphia Polyclinic Hospital, the New York Polyclinic Hospital and in Europe. His specialty was dermatology and syphilology, and since 1907 he was Professor of Dermatology in the Medical Department of the University of Arkansas.

One of his primary activities at the time of his death was the secretaryship of the Arkansas Medical Society and the editorship of the society's journal, offices which he had occupied since 1919. Always working for the best interests of his community, it was largely through his influence that the Arkansas basic science law became a reality. He was one of the originators of the Section of Dermatology of the Southern Medical Association. In 1928, Dr Bathurst was elected President of the Southern Medical Association. He served his County Medical Society as treasurer for several years. He was a member of the House of Delegates of the American Medical Association 1920-1928, 1930, 1932, and 1933. In 1924, he was elected to Fellowship in the American College of Physicians.

Although he had been aware of some cardiac involvement for about two years, Dr Bathurst did little to curtail his work. Thinking that he suffered only a passing indisposition, he absented himself from his office a day. During the night, the angel of death spread her wings.

An able dermatologist, an indefatigable worker, a progressive citizen, a gracious host, a gentleman always, William Ray Bathurst will long be revered in Arkansas medical annals.

OLIVER C MELSON, M D , F A C P ,
Governor for Arkansas

NATIONAL SCARLET FEVER PROPHYLACTIC

For Determining Susceptibility to Scarlet Fever

The Dick Test, intradermal injection of 0.1 cc Scarlet Fever Toxin, furnishes an accurate method for determining susceptibility to scarlet fever. 10 Tests 75 cents

Active Immunization

Active immunization is secured by injecting five gradually increasing doses of Scarlet Fever Toxin, first dose 500, second dose 2000, third dose 8000, fourth dose 25,000, fifth dose 80,000 skin test doses, given at intervals of one to two weeks. An average of 95% of patients with a positive Dick Test (showing susceptibility to scarlet fever) will be protected and the immunity may last for a number of years. The toxin is free from serum. Single Immunization \$1.65,—10 Immunizations \$9.25

Reliability

Not one of 2,805 susceptible nurses and internes immunized with Scarlet Fever Toxin, before they began work in hospitals for contagious diseases, contracted scarlet fever. (See International Clinics, March, 1932, page 285)

For Diagnosis of Scarlet Fever

For differential diagnosis between scarlet fever, measles, and certain erythemas, 0.1 to 0.2 cc of Scarlet Fever Antitoxin, injected intradermally into the skin of patients suspected of scarlet fever, will produce within six to twelve hours a permanent blanching around the site of injection several mm's in diameter. This is known as the Schultz Charlton Phenomenon. It is an accurate test for diagnosis of scarlet fever. One cc (5 to 10 doses) Schultz-Charlton Tests, 75 cents

National Scarlet Fever Products are prepared under license from the Scarlet Fever Committee, Inc.

THE NATIONAL DRUG COMPANY
PHILADELPHIA
U.S.A.



Mail Literature on Scarlet Fever Immunization as per adv in Annals of Internal Medicine

Name

Address

State

Date

Consultation and Advisory Service

HOSPITAL PLANNING
ORGANIZATION
MANAGEMENT
AND EQUIPMENT

•
SURVEYS CONDUCTED FOR
INDIVIDUAL HOSPITALS OR
ENTIRE COMMUNITIES

•
Office of
WILLIAM HENRY WALSH, M D
612 North Michigan Avenue
CHICAGO

The WYATT CLINIC

for

Chronic Arthritis



TUCSON, ARIZONA

Curdolac Christmas Box

(for diabetics)

ASSURES YOUR DIABETICS
A HAPPY CHRISTMAS

Beautiful to see
Good to eat
Correct in food value

—
Food values and information
on request

—
CURDOLAC FOOD CO.

Waukesha

Box 299

Wisconsin

Fellowship Key



A charm, bearing the seal of The American College of Physicians, wrought in solid gold and embossed in the College colors For Fellows only.

Price, \$7.00, postpaid

Available also in lapel button or pin with safety catch

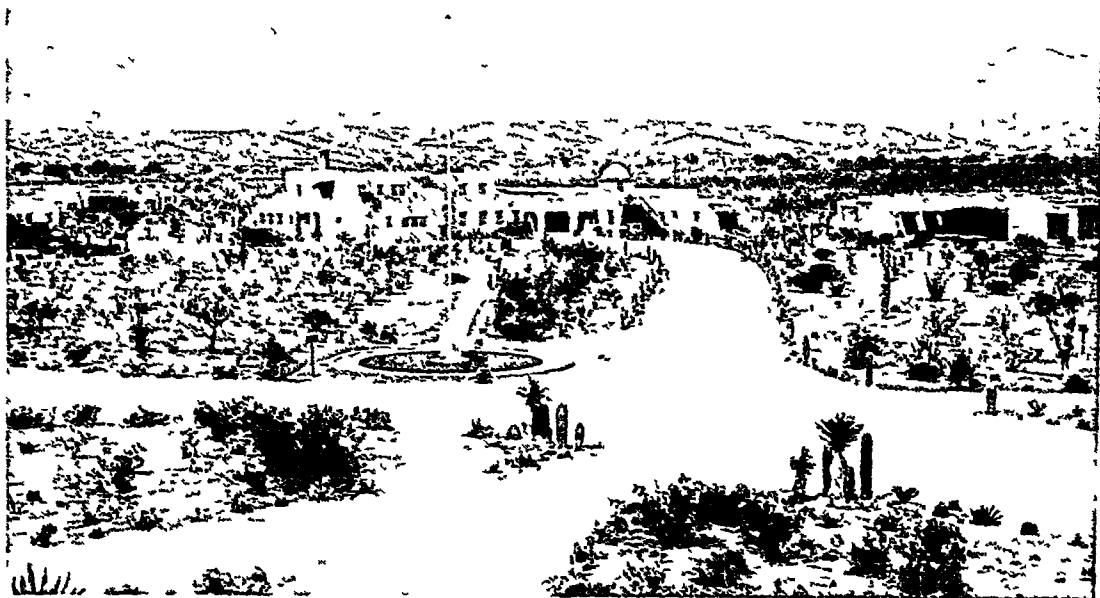
Price, \$4.00, postpaid

Send orders to

E. R. Loveland, Executive Secretary
The American College of Physicians
133-135 S. 36th Street
Philadelphia, Pa.

The Desert Sanatorium and Institute of Research

Tucson, Arizona



Altitude 2,600 feet

Entering upon its eighth season, this well-known Institution affords the facilities of modern diagnosis and treatment under unexcelled climatic conditions. Its appointments represent the acme of attractiveness, comfort and convenience. Not a hospital for the treatment of pulmonary tuberculosis, it aims at the utmost perfection of diagnosis and treatment of every condition that may be benefited by a warm, dry, sunny climate of desert type, such as chronic arthritis, sinusitis, nontuberculous pulmonary and upper respiratory complaints, arterial hypertension, cardiorenal insufficiency, etc.

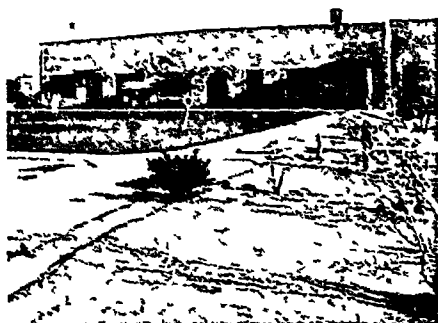
ALLEN K. KRAUSE, M.D., *Director*

W. PAUL HOLBROOK, M.D., *Physician in Chief*

VIVIAN TAPPAN, M.D., *In Charge of Pediatrics*

MAX PINNER, M.D., *Director of Laboratories*

CHARLES W. MILLS, M.D., *In Charge of Visiting Staff*



Recreation Centre



Out-Patient Clinic

WRITE FOR BOOKLET

For RATES AND OTHER INFORMATION
Address Secretary, Desert Sanatorium
Tucson, Arizona

THE POTTENGER SANATORIUM AND CLINIC FOR DISEASES OF THE CHEST

Monrovia, California



THIRTY YEARS' EXPERIENCE IN THE TREATMENT OF TUBERCULOSIS

LOCATION

Sixteen miles east of Los Angeles In the foothills of the Sierra Madre Mountains, at an elevation of 1000 feet On the main line of Santa Fe Railway Connected with Los Angeles by interurban railway and splendid boulevards

ENVIRONS

The grounds consist of a beautiful park of forty acres, in which are found a variety of native Live Oaks, subtropical trees and plants, and a profusion of beautiful shrubs and flowers Many winding walks and nooks of exquisite beauty add to its attractiveness When on exercise, patients also enjoy the beautiful trails in the adjoining canyons and mountains

MEDICAL CARE

Competent resident staff Examinations for comparison every six weeks Close medical supervision Individual needs and problems receive personal attention

THERAPEUTIC CARE

Fads are not followed, but an endeavor is made to give patients the amount of rest and exercise suited to their individual needs, the benefits of a liberal and adequate diet, such tonic measures as will increase their resistance, and other measures that will help them overcome any disturbing symptoms or complications that may arise Heliotherapy, tuberculin, pneumothorax and surgery employed whenever indicated

Weekly rates from \$25 00 up, including medical attention, medicines (except expensive remedies) and general nursing Extra charge for operative measures (except pneumothorax)

DIAGNOSTIC CLINIC

A diagnostic clinic is maintained for the study of all diseases of the chest.

F M POTTENGER, M.D., Medical Director

For Name & Address

POTTENGER SANATORIUM, Monrovia, California

THE ANALYSIS SHOWS

THE VALUABLE ALKALINE CHARACTER OF

VICHY CÉLESTINS

Natural Mineral Water

INDICATIONS

In stomach and
liver affections
and digestive disorders
in general;
in gout, arthritis
associated with uric
acidemia, uricemia,
and nephrolithiasis of
uric acid origin.



BOTTLED
AT THE SPRING
VICHY, FRANCE

ANALYSIS (GRAMS PER LITER)

Sodium bicarbonate	3.3090
Potassium bicarbonate	0.2490
Lithium bicarbonate	0.0281
Calcium bicarbonate	0.7400
Magnesium bicarbonate	0.1016
Ferrous bicarbonate	0.0012
Sodium chloride	0.3830
Sodium sulphate	0.2430
Silica	0.0300
Sodium arseniate, Phosphate and nitrate	} present

Brochure with Therapeutic Data and Medical Bibliography
sent on request.

Sole United States Agents, American Agency of French Vichy, Inc., 503 Fifth Ave., New York

THE AMERICAN COLLEGE OF PHYSICIANS

OFFICERS

President—GEORGE MORRIS PIERSOL, Philadelphia, Pa.
President-Elect—JONATHAN C. MEAKINS, Montreal, P. Q.
First Vice President—CHARLES G. JENNINGS, Detroit, Mich.
Second Vice President—NOBLE WILEY JONES, Portland, Ore.
Third Vice President—JAMES H. MEANS, Boston, Mass.
Secretary General—WM. GERRY MORGAN, Washington, D. C.
Treasurer—WM. D. STROUD, Philadelphia, Pa.
Executive Secretary—E. R. LOVELAND, Philadelphia, Pa.

REGENTS

Term Expiring 1934

JAMES S. McLESTER, Birmingham, Ala.
 WILLIAM J. KERR, San Francisco, Calif.
 JAMES ALEX. MILLER, New York, N. Y.
 SYDNEY R. MILLER, Baltimore, Md.

Term Expiring 1935

DAVID P. BARR, St. Louis, Mo.
 ARTHUR R. ELLIOTT, Chicago, Ill.
 JAMES B. HERRICK, Chicago, Ill.
 CLEMENT R. JONES, Pittsburgh, Pa.
 S. MARX WHITE, Minneapolis, Minn.

Term Expiring 1936

WALTER L. BIERRING, Des Moines, Iowa
 JOHN H. MUSSER, New Orleans, La.
 O. H. PERRY PEPPER, Philadelphia, Pa.
 FRANCIS M. POTTENGER, Monrovia, Calif.
 LUTHER F. WARREN, Brooklyn, N. Y.

Ex Officio

MAURICE C. PINCOFFS, Baltimore, Md.
 ERNEST B. BRADLEY, Lexington, Ky.

COMMITTEES

EXECUTIVE COMMITTEE

*GEO. MORRIS PIERSOL, Philadelphia, Pa.
 JONATHAN C. MEAKINS, Montreal, Que.
 WM. GERRY MORGAN, Washington, D. C.
 WM. D. STROUD, Philadelphia, Pa.
 WALTER L. BIERRING, Des Moines, Iowa
 JAMES H. MEANS, Boston, Mass.
 JAMES ALEX. MILLER, New York, N. Y.
 MAURICE C. PINCOFFS, Baltimore, Md.
 FRANCIS M. POTTENGER, Monrovia, Calif.

COMMITTEE ON ADVERTISEMENTS AND COMMERCIAL EXHIBITS

*EDWARD J. G. BEARDSLEY, Philadelphia, Pa.
 CLEMENT R. JONES, Pittsburgh, Pa.
 LUTHER F. WARREN, Brooklyn, N. Y.

COMMITTEE ON ANNALS OF INTERNAL MEDICINE

*MAURICE C. PINCOFFS, Baltimore, Md.
 (Editor)

DAVID P. BARR, St. Louis, Mo.
 JAMES H. MEANS, Boston, Mass.
 O. H. PERRY PEPPER, Philadelphia, Pa.

COMMITTEE ON CONSTITUTION AND BY-LAWS

*SYDNEY R. MILLER, Baltimore, Md.
 FRANCIS M. POTTENGER, Monrovia, Calif.
 GEORGE STROUD, Philadelphia, Pa.

COMMITTEE ON CREDENTIALS

*JOHN H. MUSSER, Baltimore, Md.
 JOHN H. MUSSER, New Orleans, La.
 CHARLES H. JENNINGS, Detroit, Mich.
 GEORGE L. CHASE, Los Angeles, Calif.
 JOHN H. MUSSER, New Orleans, La.
 S. MARX WHITE, Minneapolis, Minn.

COMMITTEE ON FINANCE

*CHARLES F. MARTIN, Montreal, Que.
 JAMES S. McLESTER, Birmingham, Ala.
 JAMES ALEX. MILLER, New York, N. Y.

COMMITTEE ON THE JOHN PHILLIPS MEMORIAL PRIZE

*DAVID P. BARR, St. Louis, Mo.
 ARTHUR R. ELLIOTT, Chicago, Ill.
 JAMES S. McLESTER, Birmingham, Ala.
 JONATHAN C. MEAKINS, Montreal, Que.
 O. H. PERRY PEPPER, Philadelphia, Pa.

COMMITTEE ON NOMINATIONS

*JOHN H. MUSSER, New Orleans, La.
 JAMES G. CARR, Chicago, Ill.
 ALLEN KRAUSE, Tucson, Ariz.
 ROGER I. LEF, Boston, Mass.
 SYDNEY R. MILLER, Baltimore, Md.

COMMITTEE ON PUBLIC RELATIONS

*CHARLES G. JENNINGS, Detroit, Mich.
 WALTER L. BIERRING, Des Moines, Iowa
 JAMES ALEX. MILLER, New York, N. Y.
 †W. BLAIR STEWART, Atlantic City, N. J.

Ex Officio

GEO. MORRIS PIERSOL, Philadelphia, Pa.

CONSULTING COMMITTEE ON CLINICAL SESSIONS

*GEO. MORRIS PIERSOL, Philadelphia, Pa.
 WM. J. KERR, San Francisco, Calif.
 JONATHAN C. MEAKINS, Montreal, Que.
 FRANCIS M. POTTENGER, Monrovia, Calif.
 S. MARX WHITE, Minneapolis, Minn.

Ex Officio

JAMES B. HERRICK, Chicago, Ill.

ANNOUNCING

IN PREPARATION

Pemberton and Osgood's

THE MEDICAL AND ORTHOPAEDIC MANAGEMENT OF CHRONIC ARTHRITIS

This is a practical exposition of the subject of chronic arthritis of particular interest to internists, general practitioners and orthopaedic surgeons

It has been written because of the convictions of the authors that chronic arthritis is largely a preventable and curable disease, and that current knowledge of the nature of the disease and of measures necessary to combat it is not as generally diffused throughout the medical profession as it should be

Probable price \$5 00



Other Important Books

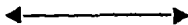
Bloomfield and Polland's

GASTRIC ANACIDITY

This book covers one of the most important and difficult clinical manifestations of the present time

"It is refreshing to read a book such as this in which an honest attempt has been made by well-qualified authors to simplify and elucidate a subject long befogged by tradition and by incomparable superficial observations. The subject has been stripped of much that was futile and imperfectly controlled. True anacidity has been clearly and simply defined, and the condition discussed in relation to gastric physiology, and certain diseased states notably pernicious anemia, gastric cancer and otherwise unexplained associated diarrhea. The wide prevalence of true anacidity and reduced acidity among otherwise normal subjects has been carefully stressed, particularly in relation to an underlying 'gastritis'."—*New England Journal of Medicine*

Price \$2 50



Clifford's

THE SPUTUM

Its Examination and Clinical Significance

"This is a most attractive book, beautifully illustrated. The subject matter is exceedingly important especially inasmuch as too many doctors have been paying too little attention to the sputum as a means of clinical and laboratory diagnosis. We can strongly recommend the book in every particular."—*Journal of Indiana Medical Association*

Price \$4 00

THE MACMILLAN COMPANY, *Publishers*

BOSTON

CHICAGO

SAN FRANCISCO

DALLAS

ATLANTA

COUNCIL ACCEPTED

THEOCALCIN

(theobromine-calcium salicylate)

A well tolerated diuretic and myocardial stimulant indicated in cardiovascular disease with, or without, renal insufficiency. . . .

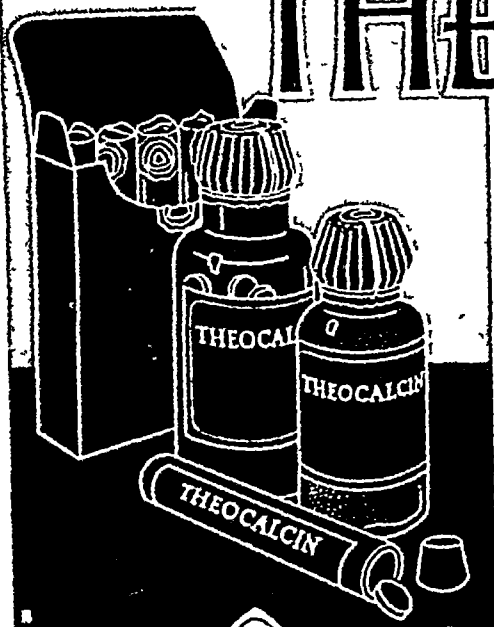
7½ grain Tablets and Powder.

DOSE: 7½ to 22½ grains t. i. d. with or directly after meals.

Literature and samples upon request.

BILHUBER-KNOLL CORP.

154 OGDEN AVENUE, - JERSEY CITY, N. J.



*Definite dosage
Ease of administration
Sensible economy*



Each pill contains 0.1 gram (1½ grains) of physiologically tested digitalis leaves. The bottled pills, too, are biologically assayed, thus giving re-assurance of their activity.

Each pill represents 15 minims of the U.S.P. tincture and permits of more accurate dosage than drops, as drops may vary in size.

Each pill contains digitalis in its completeness and not any separated or extracted part of it, to prevent the entire therapy of this valuable drug.

Please mention this package and literature sent free upon request

DAVIES, ROSE & CO., Ltd

Pharmaceutical Manufacturers

BOSTON, MASS.

U.S.

Please Mention this Journal when writing to Advertisers

Devitt's Camp, Inc.

ALLENWOOD
PENNSYLVANIA

(Tuberculosis)

*On beautiful White Deer Mountain, 20 miles southeast
of Williamsport, Pa.*

All modern methods of treatment, including heliotherapy, artificial pneumothorax, phrenic exaeresis, Jacobaeus operation, and thoracoplasty

Not operated for profit Moderate rates Modern buildings

Patients given individual attention by experienced physicians and specially trained registered nurses

The following physicians will be glad to examine patients for admittance to Camp

J M ANDERS, M D, Philadelphia, Pa
ISABEL M BALPH, M D, Philadelphia, Pa
E J G BEARDSLEY, M D, Philadelphia, Pa
WARD BRINTON, M D, Philadelphia, Pa
F W J BURGE, M D, Philadelphia, Pa
DAVID A COOPER, M D, Philadelphia, Pa
DONALD R FERGUSON, M D, Philadelphia, Pa
R₃
JOHN B FLICK, M D, Philadelphia, Pa
JOHN A KOLMER, M D, Philadelphia, Pa
W ESTELL LEE, M D, Philadelphia, Pa
A C MORGAN, M D, Philadelphia, Pa
ARTHUR W PHILLIPS, M D, Philadelphia, Pa
GEO MORRIS PIERSOL, M D, Philadelphia, Pa
E ROLAND SNADER, JR, M D, Philadelphia, Pa
MERVYN R TAYLOR, M D, Philadelphia, Pa
THOS J VISCHER, M D, Philadelphia, Pa
ALFRED W DUBBS, M D, Allentown, Pa.
A S KECH, M D, Altoona, Pa
CHARLES C HABLSTON, M D, Baltimore, Md
CHARLES S AITKEN, M D, Brookline, Pa.
J C ATWELL, M D, Butler, Pa
F DECARIO, M D, Bradford, Pa.
J W WOOD, M D, Chester, Pa

JOHN E FRETZ, M D, Easton, Pa
RICHARD R DALRYMPLE, M D, Erie, Pa
JESSE L LENKER, M D, Harrisburg, Pa
H B ANDERSON, M D, Johnstown, Pa
JOHN H ESBENSHADE, M D, Lancaster, Pa
E J WERLE, M D, Meadville, Pa
CHARLES G CRANE, M D, Newark, N J
W A WOMER, M D, New Castle, Pa
EDWARD S MCSWEENEY, M D, New York City
M THERESA SCANLAN, M D, New York City
STANLEY L WANG, M D, New York City
W R GLENNEY, M D, Pottsville, Pa
R R JONES, M D, Pittsburgh, Pa
C L PALMER, M D, Pittsburgh, Pa
A H COLWELL, M D, Pittsburgh, Pa
HOWARD U MILLER, M D, Reading, Pa
A E DAVIS, M D, Scranton, Pa
H D WILLIAMS, M D, Trenton, N J
B M ALLEN, M D, Wilmington, Del
JOHN MINOR, M D, Washington, D C
J W PEABODY, M D, Washington, D C
H R SCHREIBER, M D, Washington, D C
E W BIXBY, M D, Wilkes Barre, Pa
HARRY M READ, M D, York, Pa

BOOKLET

ROSS K CHILDERHOSE, M D
JOHN S PACKARD, M D
Associate Physicians

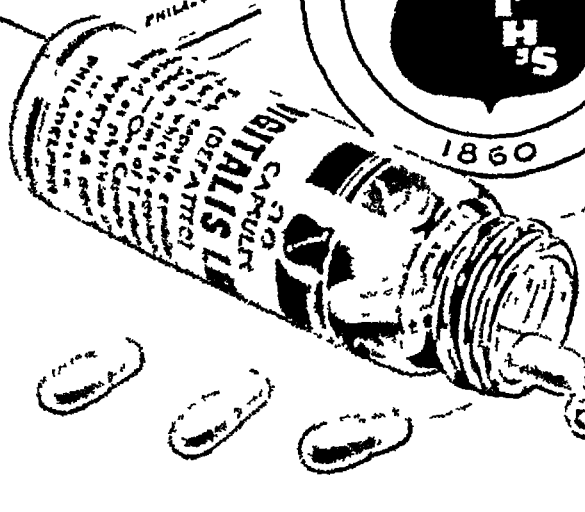
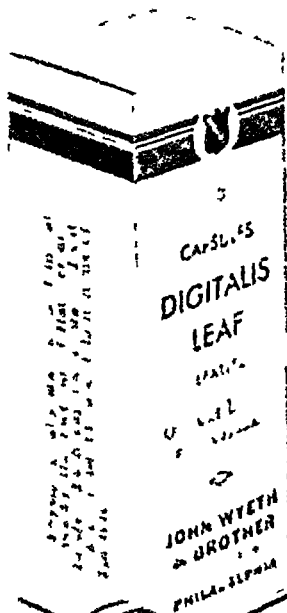
WILLIAM DEVITT, M D
*Superintendent and
Physician in Charge*

Replacing the Medicine Dropper

In digitalis medication, where accuracy of dosage is essential, the use of the medicine dropper by the patient for measuring dosage is often inadvisable. You will thus appreciate Wyeth's Capsules Digitalis Leaf (Defatted) for accuracy of dosage, convenience and uniformity. They offer several decided advantages, regardless of individual preferences as to methods of standardization.

- 1 Dependable activity of the drug.
- 2 Unvarying quantity of digitalis in each capsule.
- 3 Each capsule represents .15 minims of Tincture Digitalis U S P or 1 Cat Unit (Hatcher and Brody).
- 4 Doubly Standardized—Assayed by both the U S P Froq. Method and the Cat Method of Hatcher and Brody.
- 5 Convenient—Obviates discrepancies between minims and drops, and avoids the use of household measuring devices.

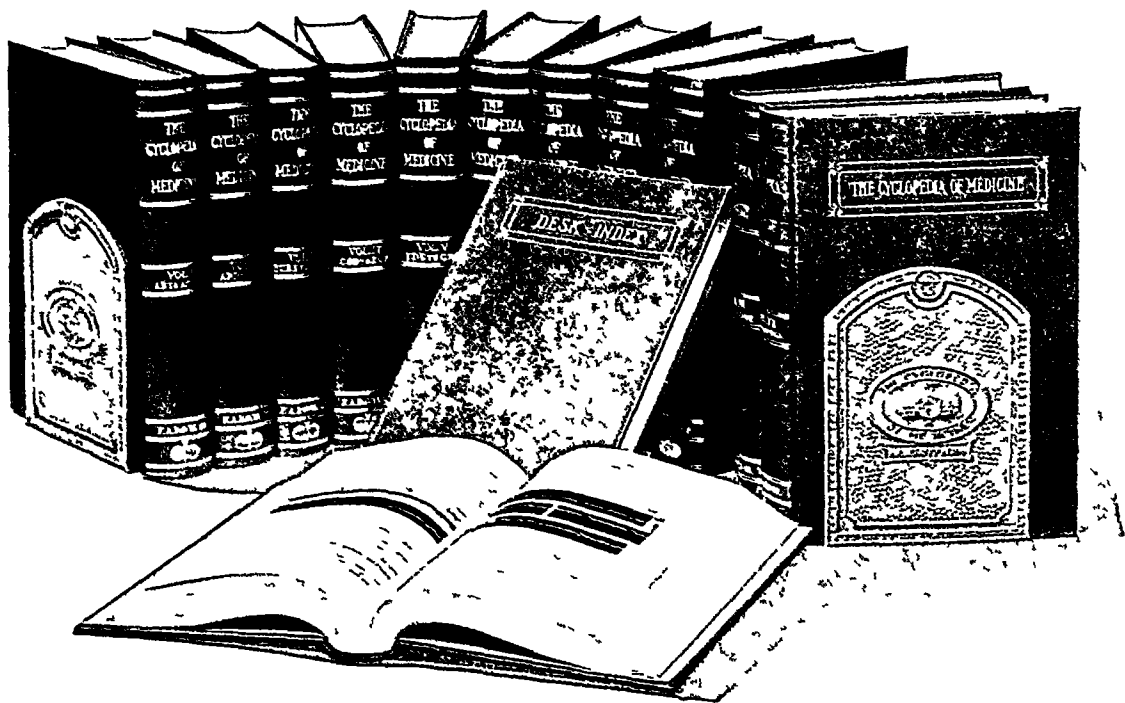
Supplied in vials of 36 capsules (sufficient for average digitalization).



**JOHN WYETH
& BROTHER, INC**

Philadelphia, Pa. and Walkerville, Ont.

700 PHYSICIANS ^{A N D} SURGEONS AT YOUR COMMAND



THE CYCLOPEDIA OF MEDICINE

GEORGE MORRIS PIERSOL, B S , M D
EDITOR-IN-CHIEF

EDWARD L BORTZ, A B , M D
ASSISTANT EDITOR

CHIEF ASSOCIATE EDITORS

W WAYNE BABCOCK, A M , M D P BROOKE BLAND, M D
CONRAD BERENS, M D FRANCIS L LEDERER, B S , M D
A GRAEME MITCHELL, M D

* 20 ASSOCIATE EDITORS AND 700 CONTRIBUTORS

The contributors have been selected from the faculties of 69 leading medical schools in the United States and Canada, 18 in England, France, Germany, Italy, Russia, Brazil and eight other foreign countries. Many are the recognized authorities in world famous clinics, research institutes, and other medical foundations. All have established reputations for outstanding work in their respective fields.

"A constantly modern library of monographs on medicine, surgery, and the specialties published in Cyclopedic form both for the convenience and economy of the profession."

* SUPPLEMENTED ANNUALLY

F. A. DAVIS COMPANY
1914-16 CHERRY STREET
PHILADELPHIA

"This is a work of outstanding importance. It is conceived along broad lines, is remarkably comprehensive, and thoroughly up to date. We have in these volumes, in readily accessible form, the marrow of Medical knowledge, an epitome of many medical libraries, a complete and authoritative exposition of the science and art of medicine. We commend the Cyclopaedia without hesitation."—*Canadian Medical Association Journal*

Please send me complete descriptive material about *The Cyclopaedia of Medicine*

Name .

Address

YOU SHOULD DEMAND THESE 3 IMPORTANT QUALITIES IN INSULIN

POTENCY CLARITY RELIABILITY

Insulin-Stearns is prepared under such exacting conditions of laboratory manufacture that it is.

Biologically exact in potency

Remarkably clear

Notably free from sting at point of injection

So anxious are Frederick Stearns & Company to provide the physician with Insulin of the highest possible dependability that they have constructed a separate Research Laboratory for the study of Insulin problems as well as for its manufacture.

We take the utmost pride in the efficiency of our Insulin Department with its modern equipment and its scientific personnel, and we are only too glad to demonstrate the step-by-step process of manufacture to interested physician visitors.

Let us send you complete literature describing Insulin-Stearns—how it is made, how it is supplied and recommended for use in actual practice. The facilities of Stearns Insulin Research Department are always at your service.

FREDERICK STEARNS & COMPANY

DETROIT, MICHIGAN, U S A.

FREDERICK STEARNS & COMPANY

Detroit Michigan

AIM 1

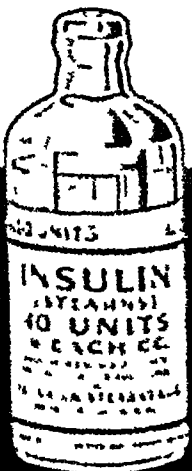
Gentlemen: I will be glad to have complete literature describing Insulin Stearns

Name

Address

City

State



ACCEPTED

Antipneumococcic Serum

Lederle

TYPES I AND II

REFINED AND CONCENTRATED

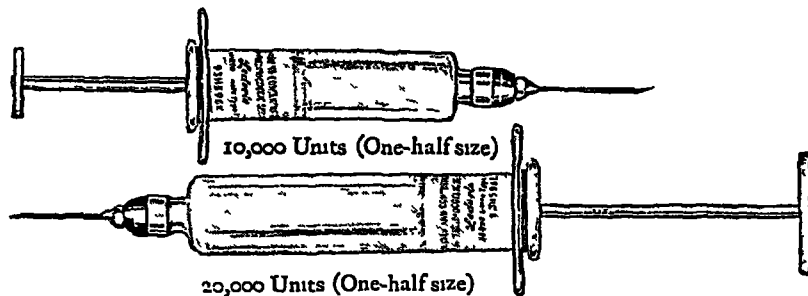
has been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

When it is considered that more than 50 per cent of all pneumonia cases between the ages of five and fifty years are either Type I or Type II, the importance of a bivalent antipneumococcic serum effective in these types will be appreciated. Between the ages of twenty and forty years the incidence of these two types is even greater.

The Department of Health of the City of New York in their Quarterly Bulletin, Vol. 1, p 30, states

"Bivalent type I and II antiserum may be used in the treatment of lobar pneumonia in adults before the infecting type is determined, as 40 to 50 per cent of the cases in this locality are caused by types I and II"

From the standpoint of lower mortality as well as economy of treatment, Bivalent Antipneumococcic Serum (Lederle) deserves your consideration



Syringe containing 10,000 units each of Type I and Type II
Syringe containing 20,000 units each of Type I and Type II

\$ 7 00
12 00

FOR RAPID TYPE DIAGNOSIS

Monovalent typing sera from rabbits, adapted for rapid typing by the Neufeld reaction as described by Sabin,* are available

One Package (5 tubes) Type I \$0 50
One Package (5 tubes) Type II 0 50

*A B Sabin, J A M A, May 20, 1933

Literature upon Request

LEDERLE LABORATORIES INC.
511 FIFTH AVENUE, NEW YORK



BEHOLD A RUGGED INDIVIDUALIST

WHEN big eyes cloud with tears and little lips frame an obstinate "I won't," a serious handicap confronts the mother in carrying out your instructions.

Sometimes there is nothing that can be done about it. Any effort on your part to make the treatment easier to follow might mean a compromise with effectiveness. But not with Haliver Oil, that is, happily, no longer the case.

Now, by prescribing Parke-Davis Haliver Oil, you can obtain full therapeutic effects from a very friendly, drops instead of terrifying the parents of cod-liver oil or other "offensive" preparations.

Parke-Davis Haliver Oil produces simplicity and ease in the question of how to administer vitamins A and D scientifically,

and at the same time *pleasantly*. This means less revolt among your younger patients—a program that mothers can follow out *to the letter*. And it also means that you can now administer vitamins A and D in a form which is really acceptable to adults who, as you know, often are the biggest babies of all when it comes to taking medicine they don't like!

Parke-Davis Haliver Oil (either Plain or with Vioosterol-250 D, in bottles or in capsule form) is available at practically all drug stores in the United States and Canada.

HALIVER OIL WITH VIOOSTEROL 250 D
 Contains 100,000 Units of Vitamin A and 25,000 Units of Vitamin D
 in 100 drops per bottle
 HALIVER OIL PLAIN
 Contains 100,000 Units of Vitamin A and 25,000 Units of Vitamin D
 in 100 drops per bottle

PARKE-DAVIS & CO., Inc., World's Largest Makers of Pharmaceutical and Biological Products

Circle 36 on Reader Service Card or Write Directly to Advertisers

a new anti-anemic preparation
with a tang and zest all its own

AUTOLYZED LIVER *Concentrate*

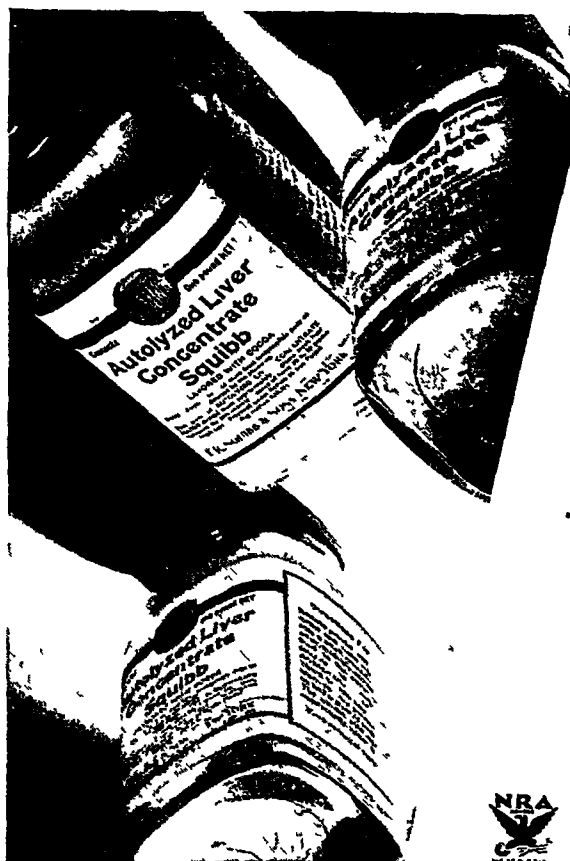
SQUIBB

AUTOLYZED LIVER CONCENTRATE SQUIBB provides all the blood regenerative properties of whole liver and yet its taste is far removed from liver itself. It has a tang and zest all its own when mixed with sweet butter and spread on bread. It can be taken also in warm bouillon or dissolved in milk.

Autolyzed Liver Concentrate is not like any other liver preparation. It is not an extract. It is prepared from whole liver, *autolyzed*, powdered and flavored with cocoa. Its use is promptly followed by a noticeable increase in red blood cells and hemoglobin and a noteworthy improvement in appetite, weight and strength.

Although primarily designed for use in the treatment of pernicious anemia, it deserves study as a diet supplement of convalescents particularly after operations where the blood loss has been severe or in the anemias of pregnancies. In addition to its anti-anemic potency it has almost twice the Vitamin B and G activity of dried yeast.

Autolyzed Liver Concentrate Squibb is economical to use—costing as little

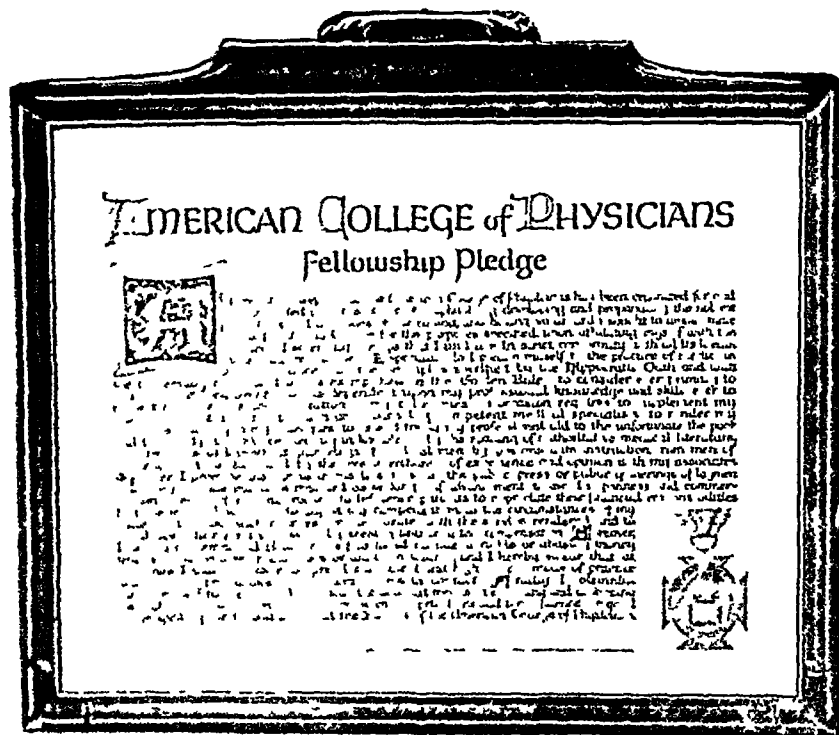


Manufactured under license to use U S
Patent Application Serial No 620,301
Marketed in ½ and 1-lb bottles Council
accepted



as 7 cents a day for the first year's treatment of an uncomplicated case of pernicious anemia. One gram of the concentrate is equal in anti-anemic potency to from 20 to 30 grams of fresh liver.

E·R·SQUIBB & SONS, NEW YORK
MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858



FELLOWSHIP
PLEDGE
of the
COLLEGE

Official Pledge
and Frame

Price \$6.00
Postpaid

Every FELLOW of The American College of Physicians should display this Pledge in his office. It is engraved on parchment, and bears the seal and colors of The College.

Send orders to E. R. LOVELAND, Executive Secretary,
The American College of Physicians, 133-135 South 36th Street,
Philadelphia, Pa.

WANTED
Copies of ANNALS
OF INTERNAL
MEDICINE

\$1.50 each for
Volume II, No. 5, November, 1928

\$.80 each for
Volume VI
No. 9, No. 10, and No. 11
March, April, and May, 1933

Address your journals to:

E. R. LOVELAND
Executive Secretary,
133-135 S. 36th Street
PHILADELPHIA, PA.

Fellowship Key



A charm, bearing the seal of The American College of Physicians; wrought in solid gold and embossed in The College colors. For Fellows only.

Price, \$7.00, postpaid

Available also in lapel button or pin with safety catch.

Price, \$4.00, postpaid

Send orders to

E. R. Loveland, Executive Secretary
The American College of Physicians
133-135 S. 36th Street
Philadelphia, Pa.

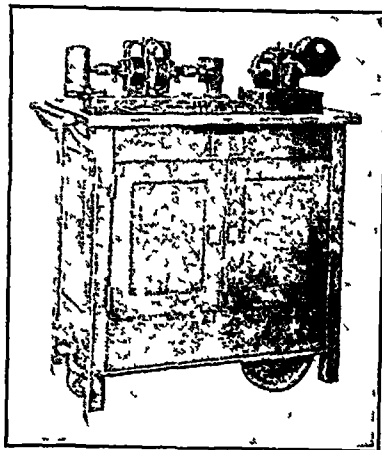
AN IMPORTANT PART of the modern periodic EXAMINATION

AS surely as "*Electrocardiography is essential to the modern study of heart disease,*" the modern study of heart condition is essential for diagnosis and treatment of the various other ills of the human body. It requires a skilled Cardiologist to correctly interpret electrocardiograms. His findings, as based upon the electrocardiogram, are "*practically speaking, infallible,*" and absolutely necessary to a complete, modern periodic examination.

**CAMBRIDGE
INSTRUMENT CO INC**

"Pioneer Manufacturers of the Electrocardiograph"

3732 Grand Central Terminal, New York City



The new "All-Electric" models are made in stationary, mobile and portable types. They are ideal instruments for hospitals, clinics and private offices, because they are always ready for instant use.

Send for Literature

H I N D L E
"ALL-ELECTRIC"
ELECTROCARDIOGRAPH

Eighteenth Annual Clinical Session THE AMERICAN COLLEGE OF PHYSICIANS

Chicago, Ill.—April 16-20, 1934

Hotel Headquarters

PALMER HOUSE

State and Monroe Sts.

Room Rates

Single - \$3.50 to \$7.00

Twin beds 6.00 to 11.00

Suites - 14.00 and up

All with private bath



Registration, General Sessions, Board Meetings and Exhibits will be conducted here.



The Palmer House

GENERAL SESSIONS will be held in the Ballroom of the Palmer House each afternoon, 2:00 P.M. to 5:30 P.M. Monday to Friday, inclusive, and in addition, from 8:00 P.M. to 10:30 P.M. Monday and Tuesday. Eminent authorities will present papers covering a broad range of topics in the field of internal medicine and affiliated specialties, such as pediatrics, gynecology, psychiatry, pathology, radiology, tuberculosis, etc.

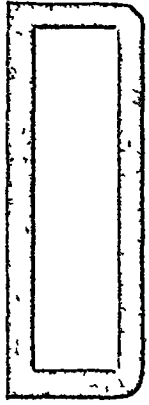
CLINICS and demonstrations will be conducted each morning Tuesday to Friday, in connection with hospitals, medical schools and laboratories.

EXHIBITS will be located in close proximity to the General Sessions. These exhibits are expected to comprise books and products in which the internist is most interested, and a representative of each attending physician will be of interest and distinct benefit to all.

TRANS-PORTATION—Reduced railroad rates on the Certificate Identification Plan will be available for participants from the United States and Canada.

WALTER M. PIERCE, President JAMES B. HERRICK, General Chairman
 Secretary, General Sessions (In Charge, Program of Clinics)
 Chicago, Ill. Chicago, Ill.

HOWARD R. LUTKENDY, Executive Sec.
 1100 Chicago Building Association Building
 1100 N. Dearborn St., Chicago, Ill.



ISPELLING DISCOMFORT *in* COLDS

CHIEF among the symptoms in the early stage of colds are backache and pain in the limbs, associated with an out-of-sorts feeling; later, particularly in coryza, a distressing headache.

Prompt relief of pain and reduction of febrile temperature help to conserve the patient's strength and thereby exercise a favorable influence upon the course of the disease.

For many years Pyramidon has proved its efficiency as an analgesic and antipyretic in the treatment of colds. The effect of one dose often extends over many hours, thus rendering frequent administration unnecessary.

Pyramidon is well tolerated both by adults and children. It does not disturb the stomach nor depress the heart or respiratory system.

Samples and Literature on Request

General Analgesic Dosage—For adults, one 5-grain tablet or 2 teaspoonfuls of Elixir of Pyramidon, repeated when pain recurs. For children of 5 years, one 1½-grain tablet or ½ teaspoonful of Elixir of Pyramidon.

How Supplied—5 grain tablets tubes of 10 and bottles of 100 1½-grain tablets bottles of 25 and 100 Elixir 2½ grains per teaspoonful, 4 oz bottles

Pyramidon
BRAND OF AMIDOPYRINE

DEPENDABLE
ANALGESIC

H. A. METZ LABORATORIES, INC., NEW YORK, N. Y.

288M

Laboratories and Factories—Rensselaer, N. Y.

1. The first step is to identify the problem or question that needs to be answered. This involves understanding the context and the specific requirements of the task.

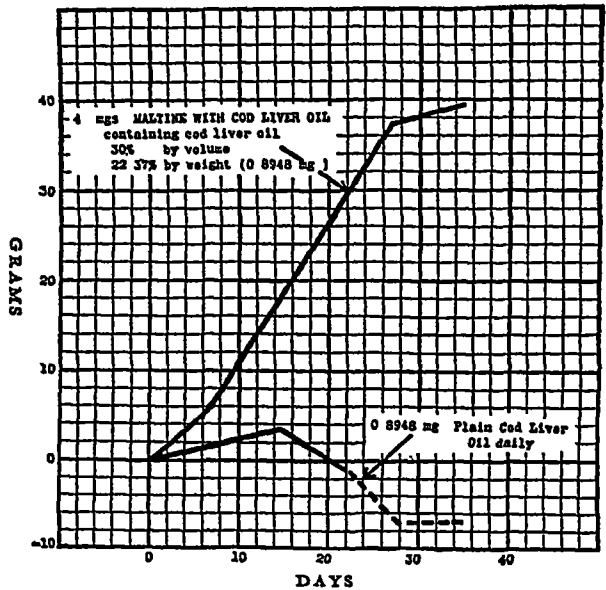
ENHANCING THE VITAMIN A VALUE OF COD LIVER OIL

THE medical profession has long used and recommended cod liver oil. More than 50 years ago, The Maltine Company, realizing the therapeutic value of cod liver oil, studied the possibility of incorporating this oil in a concentrated malt extract, hoping thereby to increase the palatability of the oil and to make available to the medical profession an emulsion which would combine the virtues of the two valuable components—MALTINE WITH COD LIVER OIL was the result.

It was found that the new MALTINE WITH COD LIVER OIL was palatable and easily tolerated by children and adults, many of whom had previously found it difficult to take plain cod liver oil. More recently, tests of various kinds, including biological and clinical, have shown that MALTINE WITH COD LIVER OIL has other characteristics, besides palatability, to recommend it.

Results of a recent investigation* have demonstrated that an actual enhancement of the value of cod liver oil occurs when the oil is administered as MALTINE WITH COD LIVER OIL.

Test animals fed a daily ration of MALTINE WITH COD LIVER OIL, containing 8948 mg of cod liver oil, made an average gain in weight of 39.7 gms during a 5 weeks' experimental period. In striking contrast to the action of these animals was the



The actual amount of cod liver oil received by the animals represented in the two curves was identical

response of litter mate controls fed the same amount of plain cod liver oil as was present in the MALTINE WITH COD LIVER OIL dosage (8948 mg). Many of the animals of the plain cod liver oil group died before the end of the experimental period with characteristic symptoms of vitamin A deficiency, while those that did live lost weight and developed more or less severe xerophthalmia prior to the end of the test. This would indicate that the value of cod liver oil is enhanced when fed in the form of MALTINE WITH COD LIVER OIL.

A chart here illustrated shows the striking difference between the average growth curves of the animals in the two groups referred to above.

MALTINE WITH COD LIVER OIL is biologically standardized and is guaranteed to contain a generous balance of Vitamins A, B, D and G. Biological and vitamin report on request. THE MALTINE COMPANY, Est. 1875, 30 Vesey Street, New York, N. Y.

*Janes, E. R., Grover, H. F., and Quinn, E. J., "A Method of Enhancing the Vitamin A Value of Cod Liver Oil," *Proc Soc for Exper Biol. and Med.*, January, 1933, p. 516.



This Trade-mark Identifies the Only Genuine

Maltine

Reg. U. S. Pat. Off.

WITH COD LIVER OIL

Introduced in 1875

"We will specify Mead's Capsules
of Viosterol in Halibut Liver Oil 250 D
when Mead puts them on the market"

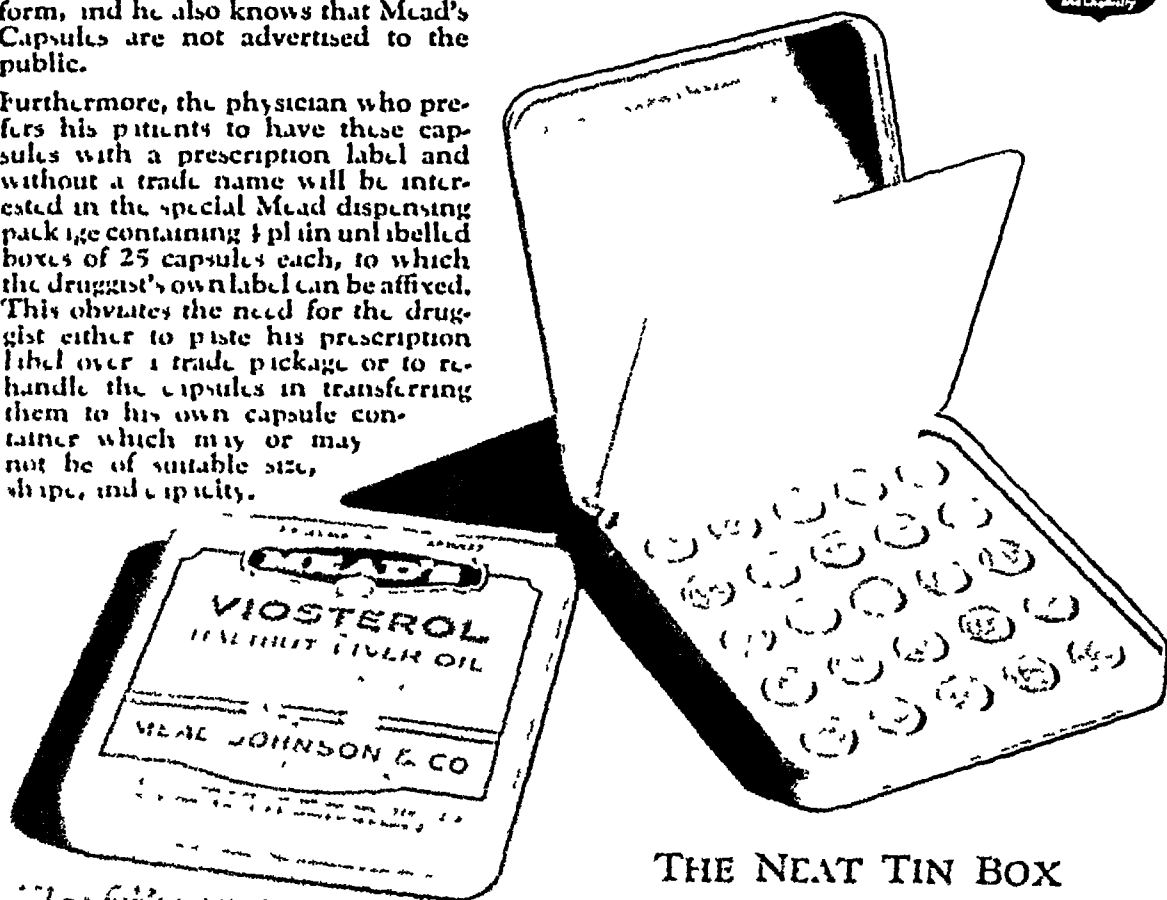
— many physicians told us.

so now—by request we offer CAPSULES

MEAD'S VIOSTEROL IN HALIBUT LIVER OIL 250 D.
Each 3-minim capsule supplies not less than 5,500 U.S.P.
Vitamin A units and 570 Steenbock Vitamin D units.

WHEN recommending Mead's Capsules, the physician is now assured of the same high grade product which is marketed by Mead in liquid form, and he also knows that Mead's Capsules are not advertised to the public.

Furthermore, the physician who prefers his patients to have these capsules with a prescription label and without a trade name will be interested in the special Mead dispensing package containing 1 plain unlabelled box of 25 capsules each, to which the druggist's own label can be affixed. This obviates the need for the druggist either to paste his prescription label over a trade package or to re-handle the capsules in transferring them to his own capsule container which may or may not be of suitable size, shape, and capacity.



THE NEAT TIN BOX

contains 25 Mead Capsules and assures maximum protection in all climates and exposure to both capsules and contents. No additional charge for this convenient line package. Specify MEAD'S—not advertised to the public.

"The fish's name is
HALIBUT"—
Specify MEAD'S

MEAD JOHNSON & COMPANY, Evansville, Indiana, U.S.A.

ANNALS OF INTERNAL MEDICINE

VOLUME 7

JANUARY, 1934

NUMBER 7

THROMBOANGIITIS OBLITERANS OF PATIENTS WITH DIABETES *

By BAYARD T. HORTON, M.D., F.A.C.P.,

and

FRANK N. ALLAN, M.D., F.A.C.P.,

Rochester, Minnesota

GANGRENE of the lower extremities in cases of diabetes is due primarily to impairment of circulation and secondarily to the effects of the diabetes on the resistance of the skin to infection. In cases of long standing, without adequate treatment, arteriosclerosis is common. It develops early in life and to a more advanced degree than in nondiabetic patients. In some cases, however, the occlusive process is of a different type. The present report, with the exception of a case reported by Adams in 1930, includes all cases of thromboangiitis obliterans complicated with diabetes observed at The Mayo Clinic. The small number indicates the rarity of the association of these diseases.

CASE I

A Russian Jew, aged 42 years, registered at The Mayo Clinic May 1, 1930. His chief complaints at the time of admission were diabetes and pain in the feet, which had been present, respectively, for five months and 18 years. Eighteen years prior to his admission, he first had noticed intermittent claudication in the calf of the left leg while drilling with the Marine Corps. The pain came on only while he was walking, and relief was obtained with rest. This symptom was slowly progressive for many years. Seven years before his admission, the pain of claudication had begun to develop after he had walked briskly two or three blocks, and was present in the muscles of both calves. Five months before his admission, a fissure had developed between the third and fourth toes of the left foot, pain while at rest had developed, and this was rather severe at the time of his examination. He had not attempted to walk during these five months, and had been in bed practically constantly. About 0.5 grain (0.032 gm.) of morphine had been required at night to relieve the pain. Fourteen years before his examination, sugar had been discovered in the urine. He had tried repeatedly to obtain life insurance following that discovery, but had been rejected by the examining physician at each attempt. He had never consulted a physician regarding the diabetes.

* Submitted for publication April 14, 1933.
From the Division of Medicine, The Mayo Clinic

until the development of the ulcer on the left foot. Polydipsia and polyuria had never been important features in his disorder. He had been taking 10 units of insulin three times a day for three weeks before his admission. He had smoked 15 cigarettes daily for many years, and had used alcohol in relatively large quantities for 12 years. There was no history of superficial phlebitis.

The man was well developed, 5 feet 6 inches (167 cm) in height and weighed 150 pounds (68 kg). He had lost 30 pounds (13.6 kg) since the development of pain in the left foot while at rest. He appeared to be exhausted. The blood pressure was 90 mm of mercury systolic, and 62 diastolic. Examination of urine gave negative results, except for the presence of albumin, graded 1. The blood counts were normal and the Wassermann test of the blood was negative. The tonsils were infected, and tonsillectomy was performed. The value for blood sugar was 0.130 gm in each 100 cc and repeated determinations of blood sugar during the patient's 27 days' stay in the hospital gave values within normal limits or only slightly above normal. The highest value for blood sugar following hospitalization was 0.170 and 0.160 gm in each 100 cc. The fissure, previously mentioned, was 1.5 cm long. Pulsations of the palpable arteries of the hands were normal except those of the right ulnar artery, which were reduced 50 per cent. Both femoral and both popliteal arteries pulsated normally. Both posterior tibial and dorsalis pedis arteries were occluded. Pallor of the feet followed elevation of them, that of the right foot was graded 3 and that of the left foot, 2. Rubor, graded 2, was present when the feet were dependent. Roentgenograms of the legs gave evidence of mild arteriosclerosis. The vasomotor index of the left foot ranged from 1.3 to 2 and that of the right foot from 1.8 to 2.4 (low values).

The diet prescribed consisted of 73 gm of carbohydrate, 53 gm of protein, and 176 gm of fat. The patient continued to take 10 units of insulin three times daily. During his stay of 27 days in the hospital he received seven intravenous injections of typhoid vaccine, and at the time of his dismissal the ulcer had entirely healed. He was dismissed with directions to take daily, 77 gm of carbohydrate, 50 gm of protein, 144 gm of fat, and 10 units of insulin. The patient died two years later of morphine addiction combined with an acute psychosis.

The diagnosis of thromboangitis obliterans was valid because the patient was young (aged 24 years) at the time of onset of symptoms, because the circulation in the feet was diminished, and because pulsations of the right ulnar artery were impaired. The presence of slight grades of calcification of the arteries of the legs indicated a mixed occlusive process of the vessels. The arteriosclerotic changes were probably accelerated by the presence of diabetes.

CASE II

A white male, 47 years of English-American stock, was admitted to hospital in 1929. He had been complaining of pain in the left leg and foot, and a gangrenous ulcer on the left foot. He had begun to have pains of claudication in the left foot in April 1928, and the pains were more severe at rest and the trouble had become worse, so that he was unable to walk more than a few minutes at a time. A year before admission a corn had been removed from the left foot, and the ulcer on the left foot had failed to heal. A diagnosis of thromboangitis obliterans was made in September 1929, because of the discovery of calcification of the arteries of the legs. He had been treated for a short time, but the ulcer on the left foot was not healed. He had been eating ordinary food, and had been taking 10 units of insulin three times a day. The patient was given the ordinary treatment for thromboangitis obliterans, and the ulcer on the left foot was not healed.

on two occasions, and the value for blood sugar was 130 mg for each 100 c c, also on two occasions. In order to verify the diagnosis of diabetes a sugar tolerance test was made. The response was typical of mild diabetes. The concentration of sugar in the blood rose from 0.120 to 0.240 gm in each 100 c c in half an hour, and to 0.310 in two hours. From this time on restriction of the carbohydrate of the diet was advised. The patient had been smoking 40 cigarettes a day for 10 years. He had had symptoms suggesting renal colic, but his previous health had otherwise been satisfactory.

Examination at the clinic disclosed absence of pulsations of the arteries of the left foot. Pulsations of the usually palpable arteries of the other extremities appeared normal. There was abnormal pallor of the foot when elevated. Roentgenologic examination of the feet and legs did not give evidence of calcification of the vessels. The other examinations gave negative results.

Efforts were made to improve the circulation of the foot by induction of fever and other measures. The patient went home, but returned in six weeks with gangrene of the left foot, suffering intense pain. A Gritti-Stokes amputation of the leg was performed September 29, 1930. The following day, sugar appeared in the urine, and treatment with insulin was instituted. The amount of insulin had to be increased daily until the ninth day, when a dose of 80 units was reached. The amount of insulin given daily had gradually been reduced to 15 units on the twenty-fourth day after operation. The stump failed to heal, and it was necessary to amputate again, through the thigh, November 3, 1930. Aggravation of the diabetes was again encountered, and larger doses of insulin were required for 10 days, but the dose given was not so large as after the first operation. The use of insulin was discontinued on the eighteenth day after the second amputation. Satisfactory healing of the wound finally occurred. The urine remained free from sugar, and the concentration of sugar in the blood remained normal on a diet of 135 gm of carbohydrate. Only sugar and sweet desserts were omitted from the diet. The diabetes had again become latent.

The patient was seen again July 19, 1932. At this time he was in good health. The stump of the left thigh was in good condition. The right foot seemed normal except for slight diminution in the pulsations in the dorsalis pedis and posterior tibial arteries. The color of the foot was normal. Dietary regulation had maintained control of the diabetes. The patient was advised to continue precautions to protect his foot from injury. He was also advised not to smoke.

Concerning case 2, attention should be directed to the fact that before operation diabetes was practically latent, although the patient had been on an ordinary diet for a long period and the urine was free from sugar, except for a trace on rare occasions. The value for blood sugar was just on the borderline of the normal range. Under these conditions the existence of diabetes might be doubted, or it might be thought that diabetes, if present, was so mild as to be of no significance. The diagnosis of diabetes was confirmed by the glucose tolerance test, and the events following operation showed that the condition was by no means benign. Under ordinary conditions, the diabetes was so mild it could be detected only by a glucose tolerance test, following the surgical operation it was changed to diabetes of severest grade. The amount of insulin needed was as high as that required in the most severe cases.

The diagnosis of thromboangitis obliterans was based on the age of the patient, absence of calcification of the arteries of the affected extremity, and a history of excessive use of cigarettes. This diagnosis was confirmed by a

study of the anterior and posterior tibial arteries of the amputated extremity. Numerous segments were occluded with old and recent thrombi. The recent lesions were characterized by a chronic inflammatory process. Giant cells were present in small numbers in some of the small, occluded vessels. Calcification of the walls of the vessels was not encountered in the sections studied.

CASE III

A Russian Jew, aged 38 years, registered at the clinic July 9, 1926, because of the following conditions: diabetes mellitus which had been present in mild form for seven years, twitching and coarse jerking movements involving various groups of muscles which had been present for one year, and intermittent pain of claudication of the left leg, which had developed three months before admission. At the time the diabetes was discovered, the man's intake of carbohydrate had been restricted, and the urine at once had become free of sugar and had remained so for two years. He then had ceased to follow the prescribed diet, and glycosuria again had developed. He had then been given 18 units of insulin daily, and a diet of fats 165 gm., protein 65 gm., and carbohydrates 150 gm., which he had continued to follow. The jerking and twitching of the various groups of muscles, especially of the muscles of the legs and arms, usually developed at night, frequently after a hard day's work. This had not been progressive. The pain of intermittent claudication in the muscles of the left calf had become progressively worse. It was definitely associated with exercise. It came on after walking a half block to a block, with further walking, the pain became worse, spread up the leg, and the man became lame. Rest gave relief of symptoms. There was no history of phlebitis. The patient smoked about 18 cigarettes daily.

General examination gave essentially negative results, except that the left foot was distinctly colder than the right. Pulsations, however, were present in both dorsalis pedis and posterior tibial arteries, and no definite rubor or blanching of the feet was observed. Unfortunately, no record was made of the pulsations in the upper extremities at that time, for we were not as familiar with thromboangitis obliterans as we are at present. The blood pressure was 120 mm. of mercury systolic, and 70 diastolic. The urine at the time of the patient's admission was negative, the blood counts were normal and the Wassermann test of the blood was negative. The value of blood sugar was 0.110 gm. in each 100 cc. Roentgenograms of the thorax, teeth and of the accessory sinuses gave negative results. Roentgenograms of the extremities were not made. Neurologic examination gave objectively negative results. Foci of infection were not present. The sugar tolerance test gave evidence of mild diabetes mellitus.

The patient was sent home, with directions to take 72 gm. of carbohydrate, 50 gm. of protein, and 150 gm. of fat daily, without insulin. We have been unable to obtain further follow-up letters from this patient.

A tentative diagnosis of early thromboangitis obliterans and diabetes mellitus was made. The history of intermittent claudication alone suggests a localized vascular process in the left leg, which apparently involved the posterior tibial artery or arteries. The age and race of the patient aided in the diagnosis.

CASE IV

Received at the clinic, July 23, 1930. Examinations by Dr. Frank N. Allan, Dr. Bayard T. Horton, and Dr. J. H. Brown.

ulcer had developed on the first toe at that time. Superficial phlebitis of the left leg first had been observed three years before the patient's admission to the clinic, and a similar condition of the right leg, one year before his admission to the clinic. Intermittent pain of claudication, involving the arch of the right foot, had been observed for one year. This had become progressively worse, and the man had been able to walk only a half block without pain at the time the ulcer on the right great toe developed. He had smoked 20 cigarettes daily for 20 years.

Physical examination was negative, except with respect to the lower extremities. There was an ulcer of the right great toe, and pulsations could not be felt in the right dorsalis pedis and posterior tibial arteries. The arteries of the left lower extremity pulsated normally, except the left dorsalis pedis and posterior tibial arteries, where the pulsations were slightly reduced. Pulsations of the vessels of the hand were normal. Rubor, graded 1 to 2, of the toes of both feet was present when the feet were dependent, and pallor, graded 1 to 2, of the toes of both feet was present when the feet were elevated. There was intermittent glycosuria, and the glucose tolerance curve gave evidence of mild diabetes. A restricted diet was instituted. Fever was induced by giving typhoid vaccine intravenously and sulphur-in-oil intramuscularly. Improvement gradually ensued, there was complete relief of the pain while at rest, the ulcer healed, and the patient was dismissed in two months in satisfactory condition.

The second admission was March 14, 1931. During the interval the man's condition had been satisfactory. There was no change in the pulsations of the peripheral blood vessels. The ulcer had healed, there was an occasional twinge of pain in this area. The vasomotor response to induction of fever caused an average increase of 10°C in the temperature of the toes. The patient was considered to be in satisfactory condition for lumbar sympathetic ganglionectomy, but he felt that he was getting along so well he wished to postpone this procedure.

The third admission was September 1, 1931. The ulcer had remained healed. Claudication appeared after the patient had walked two or three blocks, and his activities had been kept at about 50 per cent of normal. The feet were warm, growth of nails was normal, and there was no change in the pulsations of the peripheral arteries. The diabetes was well controlled by diet, and the case was considered to be an instance of compensated thromboangitis obliterans.

The patient's fourth admission was May 11, 1932. At this time the pulsations of the posterior tibial and dorsalis pedis arteries of the right foot were intermittent and reduced. There was claudication in the right leg after walking one to three blocks. A small area of superficial phlebitis was present on this leg. There were no symptoms of diabetes. The diabetes continued to be controlled with dietetic restrictions. The patient was given four injections of typhoid vaccine for production of fever, with satisfactory effects on the claudication.

This is a typical example of slowly progressive thromboangitis obliterans. Closure of the vessels was not so rapid but that collateral circulation could keep pace. The patient reacted extremely well to fever therapy. The ischemic ulcer healed rapidly, and objective evidence of improvement was noted in the circulation of the extremities.

The diabetes was mild and easily controlled. Much will depend on the willingness of the patient to continue with a restricted diet. Any excess of carbohydrates undoubtedly will make this patient more liable to cutaneous infection in the presence of the somewhat diminished circulation.

One additional case of thromboangitis obliterans with diabetes has been observed at the clinic, and was reported by Adams¹ in 1930. Two ad-

ditional subjects, both Russian Jews, aged respectively 31 and 44 years, both with diabetes, were also thought to have thromboangitis obliterans, but the clinical evidence was not sufficient to allow a positive diagnosis of thromboangitis obliterans to be made, for that reason these cases have not been included in the present report

SUMMARY

Three Russian Jews and a man of English-American extraction, aged respectively 42, 47, 38, and 42 years, had thromboangitis obliterans and diabetes mellitus. All were excessive smokers of cigarettes. Thromboangitis obliterans in these subjects did not seem to be accentuated by the presence of diabetes mellitus.

BIBLIOGRAPHY

- 1 ADAMS, S F Case of diabetes mellitus with thromboangitis obliterans, *Med Clin N Am*, 1930, xiv, 581-583

HUMAN CONSTITUTION.

A STUDY OF THE CORRELATIONS BETWEEN PHYSICAL ASPECTS OF THE BODY AND SUSCEPTIBILITY TO CERTAIN DISEASES *

By WALTER FREEMAN, M D , F A C P , *Washington, D C*

THERE is a saying One man's meat is another man's poison This will be recognized as a crude statement of the constitutional peculiarities and differences of various members of the human species, and is another indication of the penetrating insight of the folk-lore poet that precedes the slow march of science Where science goes beyond the philosopher is in asking why and then proceeding to find the answer

For the purposes of this study we may paraphrase the saying somewhat as follows The more nearly two individuals resemble each other, the greater are their chances of developing the same disease It is highly probable for instance that we are all exposed to tuberculosis at some time in our lives, yet only a certain proportion of us develop the disease Among those that do there is often a general family resemblance We go through life on very much the same routine of eating, working and sleeping, and some of us develop hypertensive disease and others acquire gall-stones, and some develop diabetes or cancer A study of the constitutional factors in patients suffering from these diseases will often show underlying trends in them that bring them into rather close relationship with one another, so that Draper¹ has been able to delineate an ulcer race, a gall-bladder race, a pernicious anemia race It is easy to ask why, but the answer lies buried so deep in the peculiarities of structural make-up, of chemical and metabolic processes, and of psychologic outlooks, that go to make up the total personality, that we are, even in the beginning, somewhat baffled by the magnitude of the problem of constitution

The constitution of an individual may be defined as the sum-total of all his peculiarities and potentialities Just how much is a matter of genes and how much is conditioned by early environment cannot be determined accurately After birth the body increases in size only about 20 or 30 times, whereas the increase from the ovum to the mature fetus may be a matter of billions The changes imposed upon the constitution after childhood are certainly minimal The equipment with which an individual starts life, his fundamental constitution, is largely determined by heredity, and Pende² has likened constitution to a three-cornered pyramid the base of which

* Presented before the American College of Physicians, Montreal, Canada, February 9, 1933

From Blackburn Laboratory, the Department of Neurology, George Washington University, and the Department of Biology of the School of Hygiene and Public Health, Johns Hopkins University Aided by a grant from the Josiah Macy, Jr Foundation

represents heredity and the three sides, respectively, the structural, the chemical and the psychological aspects of the personality

The chemical side of the personality is probably the most important from the standpoint of general medicine, since immunities and susceptibilities to disease are determined largely in this manner, not to mention the various metabolic processes, endocrine activities and other organic reactions. The correlation of different constitutional peculiarities of the individual, his physical architecture and his personality trends, with his susceptibilities and resistances to disease, has formed the basis of a number of interesting studies. Three years ago I³ reported some correlations between psychologic reaction type and susceptibility to certain diseases, and it is possible now to amplify the previous findings by demonstrating some correlations between body type and susceptibilities to the same diseases. For this purpose, the material, consisting of some 1260 autopsied cases, has been divided into four groups corresponding to Kretschmer's⁴ classification, asthenic, athletic, pyknic and dysplastic. The asthenic type is seen in the long thin individual with poorly developed muscles and a narrow costal angle. The pyknic type has a short broad body with a round head, and, as Kretschmer calls it, a magnificent paunch. The athletic type lies in between. It is not particularly distinguished as a separate group, since there are various types of athletes extending from the distance runner to the weight thrower. As a rule, however, the proportions of the athlete are more harmonious than those of the other two groups. The dysplastic individual does not fit into any of the above three groups by reason of a combination of pyknic and asthenic traits, or because of abnormalities of body that stamp him as distinctly freakish. Conditions are similar, in the main, for women, although the pyknic type is often taller and larger all around than is the athletic.

The distribution of the patients is given in table 1, which shows the per-

TABLE I
Distribution of Physical Types in 1081 Cases

Asthenic	31.8%
Athletic	34.8%
Pyknic	14.9%
Dysplastic	13.8%
Unknown (no data)	4.7%
Total	100%

centage of individuals falling in each class. It will be noted that the asthenic and athletic are about equal in number, and the pyknics half as many, the dysplastics making up only about one-eighth of the total cases. Allowance must be made for this uneven distribution in comparing the ratios of the various diseases and lesions found in subsequent tables.

A comparison of the physical and psychological types is of interest and tends to confirm the findings of Kretschmer (Figure 1). The asthenic habitus is most often associated with the shut-in schizoid personality trend,

while the pyknic habitus and the extrovert, cycloid personality run together. Furthermore, there is quite a predominance of dysplastic individuals among the epileptics, and the paranoids show a rather even distribution among

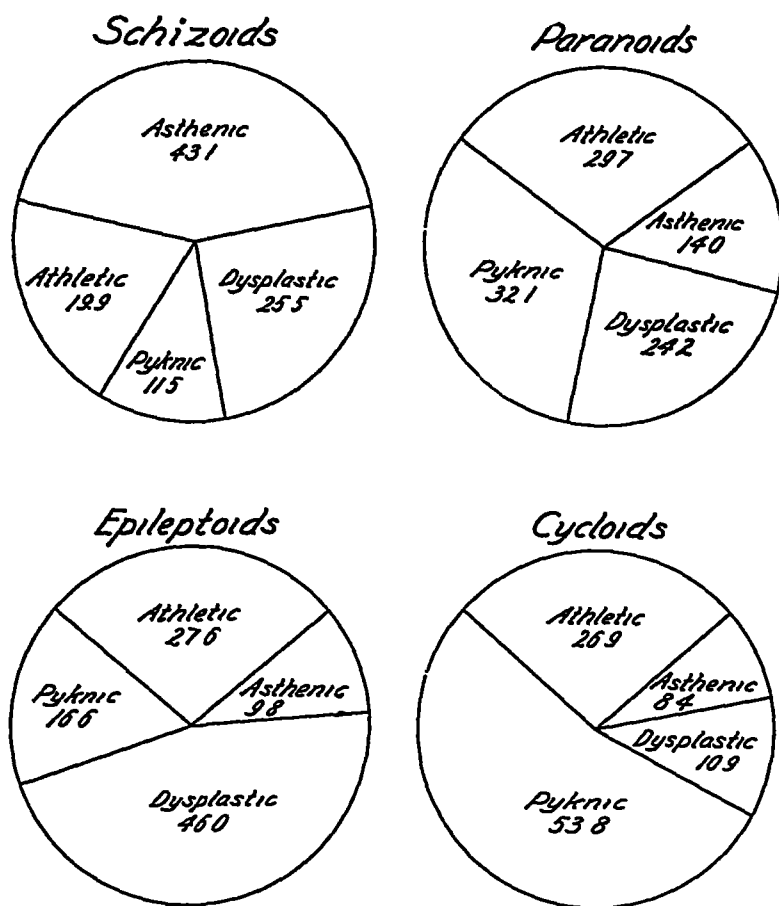


FIG 1 Pie diagrams indicating physical make-up of the several psychologic classes

classes with pyknics and athletics almost even. The small percentage of asthenics among the cycloids and of pyknics among the schizoids forms the reverse of the preceding picture. The individuals have been grouped according to body type and personality type alone, without regard to sex or race, and independently of the supposed cause of the psychosis. Our studies are showing that only minor differences are apparent between the symptomatic and the idiopathic psychoses as far as the personality types and body types are concerned, and that constitution transcends race, sex and age.

The distribution of a number of disease entities and of pathologic lesions is given in the accompanying table (Table 2). It must be called to mind that these percentages are not weighted, so that the relative incidence of the various lesions is not shown, but even so, certain findings stand out that indicate rather pronounced irregularities in the distribution of certain diseases. The high proportion of asthenics among the tuberculous, and of

TABLE II

Distribution of Disease Classes According to Body Types, Both Sexes, All Races

	Total Number of Cases	Percentage of Cases in Body Groups				
		Not differ- entiated	Asthenic	Athletic	Pyknic	Dysplastic
All cases 1260	1260	4.7	31.8	34.8	14.9	13.8
<i>Cardio-vascular disease</i>						
Chronic myocarditis, sclerosis, fibrosis	488	7.0	26.6	37.1	16.2	13.1
Coronary thrombosis, infarction, aneurysm, rupture	84	3.6	19.0	36.9	22.6	17.9
Pericarditis, acute, adhesive, chronic	88	2.3	34.1	35.2	11.4	17.0
Valvular disease, endocarditis, aortic and mitral stenosis	271	3.7	22.5	40.2	15.9	17.7
Cardiac syphilis	82	1.2	30.5	39.0	17.1	12.2
Aortic aneurysm, luetic or senile	32	—	9.4	43.7	34.4	12.5
Vascular thrombosis of aorta, lung, spleen, small intestine	192	3.1	20.3	39.1	20.8	16.7
<i>Nervous diseases</i>						
Cerebral hemorrhage	42	—	9.5	54.8	26.2	9.5
Cerebral thrombosis, infarction	316	5.4	23.4	40.2	16.1	14.9
Neurosyphilis	279	5.7	31.5	39.8	12.2	10.8
Encephalitis, meningitis	105	4.8	35.2	30.5	16.2	13.3
Pachymeningitis, subdural hematoma	95	6.3	27.4	45.2	5.3	15.8
Cerebral malformations, hydrocephalus, diffuse gliosis	75	5.3	22.7	30.7	12.0	29.3
<i>Neoplastic disease</i>						
Primary carcinoma all organs	127	7.0	27.1	38.8	12.4	14.7
<i>Respiratory diseases</i>						
Active tuberculosis	179	3.4	62.5	16.2	3.9	14.0
Healed tuberculosis	313	4.5	31.6	32.3	15.0	16.6
Lobar pneumonia and influenza	72	2.8	27.8	40.2	13.9	15.3
Bronchopneumonia	614	6.0	33.2	37.9	10.7	12.2
Pulmonary thrombosis, infarction, hemorrhage	126	1.6	19.8	38.9	24.6	15.1
Pulmonary abscess and gangrene	70	5.7	44.2	32.9	2.9	14.3
Bronchiectasis and syphilis	87	9.2	31.0	41.5	5.7	12.6

pyknics suffering pancreatic hemorrhage, is worthy of note, as well as the preponderance of intestinal disorders such as hernia, foreign bodies and intestinal gangrene among the athletic. A few other disorders, in which one special body type contains more than 40 per cent of the total lesions, may be mentioned. Cardiac valvular disease, aortic aneurysm, cerebral thrombosis and hemorrhage, nephritis, pyelonephritis, prostatic hypertrophy and malignancy, pituitary tumors, goiter and subdural hematoma occur in considerable numbers in the athletic type. Pulmonary abscess and gangrene as well as pulmonary and intestinal tuberculosis pick out especially the asthenic type, while pyknics comprise a rather high percentage of diabetics. The dysplastics are so few in number that they do not show any strikingly high percentages for any lesions.

Those diseases showing a relatively low distribution among certain body types may also be mentioned, taking 10 per cent as the dividing line. Few

TABLE II (Continued)

	Total Number of Cases	Percentage of Cases in Body Groups				
		Not differ- entiated	Asthenic	Athletic	Pyknic	Dysplastic
All cases 1260	1260	4 7	31 8	34 8	14 9	13 8
<i>Gastrointestinal diseases</i>						
Ulcers of stomach and intestine, enteritis	82	—	31 7	34 1	11 0	23 2
Carcinoma of stomach	30	—	33 3	30 3	13 3	23 3
Intestinal tuberculosis	89	1 1	75 3	13 5	1 1	9 0
Hernia, all types	14	7 1	14 3	71 4	—	7 1
Thrombosis, infarction, rupture, gangrene of small intestine	8	12 5	—	62 5	12 5	12 5
Foreign bodies	7	—	28 6	42 9	14 3	14 3
Chronic colitis	55	—	38 1	27 3	16 4	18 2
Cirrhosis of liver, mostly mild	289	3 1	26 6	34 4	18 3	17 6
Chronic cholecystitis with or without stones	264	5 3	29 5	35 7	14 0	15 5
Diabetes mellitus	17	5 9	11 8	29 4	41 1	11 8
Hemorrhagic pancreatitis	31	3 2	12 9	22 6	54 8	6 5
Carcinoma of biliary passages	15	6 7	20 0	46 7	13 4	13 4
<i>Urogenital diseases</i>						
Nephritis	74	4 1	32 4	40 5	6 8	16 2
Nephrosclerosis, fibrosis, infarcts, sclerosis, chronic inflammation of gonads	922	5 0	28 2	38 2	14 2	14 4
Pyelonephritis, abscess	119	7 6	30 3	41 1	10 9	10 1
Lithiasis	56	1 8	19 6	25 0	30 4	23 2
Cystitis	62	6 5	25 8	38 7	17 7	11 3
Prostatic hypertrophy	199	3 5	25 1	42 7	15 6	13 1
Carcinoma of prostate and bladder	22	4 5	31 8	40 9	4 5	18 2
Uterine fibroids	151	4 0	25 2	35 8	21 9	13 2
Ovarian cysts	83	2 4	34 9	32 5	18 1	12 0
Urogenital malformations	58	1 7	27 6	25 9	12 1	32 8
<i>Endocrine diseases</i>						
Pituitary tumors	52	3 8	15 4	51 9	15 4	13 5
Goiter	105	3 8	27 6	40 0	14 3	14 3
Persistent thymus	168	—	31 0	36 3	11 3	21 4
Adrenal hemorrhage	16	6 3	37 5	37 5	6 3	12 5
Adrenal adenomata and hypernephromata	45	—	31 1	28 9	15 6	24 4

aortic aneurysms and cerebral hemorrhages occur in asthenic individuals. Pulmonary abscess and gangrene and bronchiectasis, as well as tuberculosis of the lungs, are rare in pyknics, few cases of nephritis, of prostatic carcinoma, of pachymeningitis and of adrenal hemorrhage occur in pyknics. The dysplastic group is represented by relatively few instances of hernia and of hemorrhagic pancreatitis. The athletic group has a fairly large proportion of all the different lesions both on account of the size of the group and because it stands more or less in mid-position between contrasting body types.

In order to contrast the distribution of various groups of diseases among the four body types, figure 2 has been constructed. The relatively even distribution of the acute infectious disorders (compare with table 1) lends added weight to the differences observed in the other categories, since the

acute infections as such are more strictly conditioned by external factors (microorganisms) than by constitutional traits

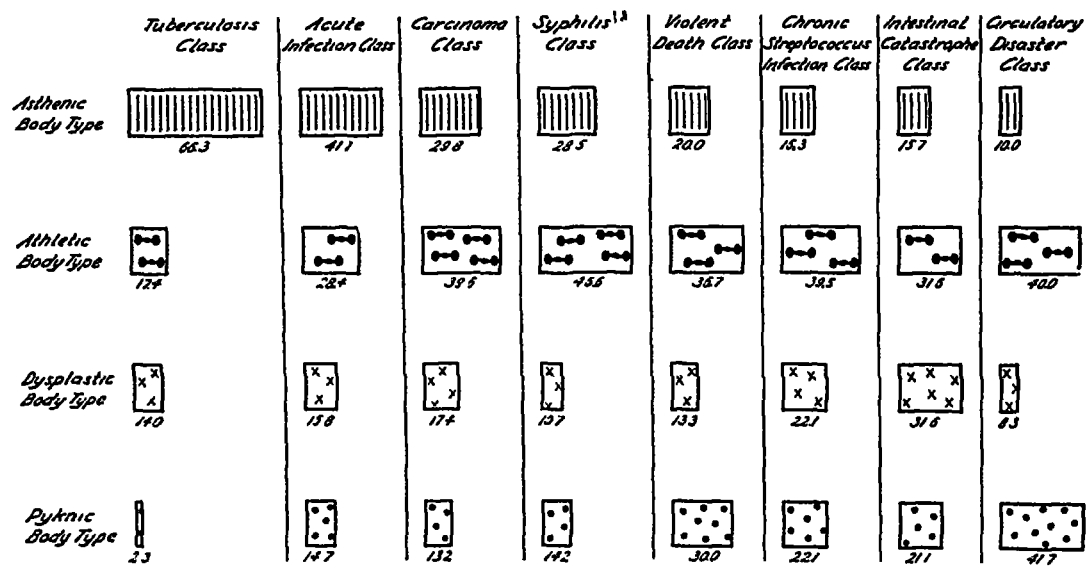


FIG 2 DISEASE TYPE AND BODY TYPE

Percentage of individuals of different body types having a specified disease type Both sexes and all races are included, but only those individuals that have been differentiated as to both body type and disease type Individuals listed as having more than one disease are classified in only the more important group The order of importance of disease groups has been taken to be the following Tuberculosis takes precedence over all other groups, syphilis next, then carcinoma, circulatory disease, streptococcal infections, intestinal disease, violent deaths, and acute infections, in the order named Therefore, tuberculosis and syphilis occurring together would be counted only in the tuberculosis group, as would tuberculosis and circulatory disease Syphilis and violent death would be classified only under syphilis The second disease in each case is ignored

Comparing the distribution of separate disease entities according to physical type with the distribution of the same diseases according to psychologic type brings out the noteworthy fact that distinctions are sharper in the latter This would seem to indicate that the personality of the individual is more closely linked with his immunologic attributes than is his physical build

Finally, from a study of the combined figures, a reconstruction of the constitutional pyramid of Pende, certain constellations may be picked out as contrasting examples of human biotypes The asthenic-tuberculous-schizoid contrasts with the pyknic-angiopathic-cycloid, and both of them with the dysplastic-exudative-epileptoid, while another less striking example is the athletic-paranoid group showing decided tendencies toward malignant disease and chronic streptococcus infections

The necessity for a study of the patient as a whole is again emphasized This contribution shows that there are certain diseases that show a predilection for one physical type or another, just as the former study showed that some diseases fell more heavily on one psychological type than another Rather definite relationships between mental and physical types complete the

triangle of constitution, and it is possible to erect certain constellations comprising all three facets of the individual's total personality

The author is indebted to Miss Marjorie Gooch, Associate in the Department of Neurology, George Washington University, for the statistical handling of the data

REFERENCES

- 1 DRAPER, G Disease and the man, 1930, Macmillan Company, New York
- 2 PENDE, N Constitutional inadequacies (translated by S Naccarati), 1928, Lea and Febiger, Philadelphia
- 3 FREEMAN, W Psychological panel in diagnosis and prognosis, correlation of personality type with susceptibility to disease, based on 1400 necropsies, *ANN INT MED*, 1930, *iv*, 29-38
- 4 KRETSCHMER, E Physique and character, 1925, Harcourt, Brace, and Company, New York

PAROXYSMAL VENTRICULAR TACHYCARDIA: AN ETIOLOGICAL STUDY WITH SPECIAL REFERENCE TO THE TYPE[†]

By CLAYTON J LUNDY, M D , and LAWRENCE L McLELLAN, M D ,
Chicago, Illinois

PAROXYSMAL TACHYCARDIA of ventricular origin is a cardiac disorder which, because of its severity, deserves and has received much study. There are, however, questions as to its mechanism and etiology that are still unanswered. This is our warrant for reporting three cases and for recording the results of a survey of the literature on this subject. We have endeavored to get facts as to the causes that excite its outbreak as well as to the nature of the heart disease which underlies this condition. This survey may also be helpful in an attempt to correlate these findings with a classification of the various types of the arrhythmia, and thus bring about a closer relationship to the exciting causes and foundation etiological factors.

CASE I

A boy, A D , 16 years of age, presented himself at the Cental Free Dispensary, January 26, 1930, complaining of spells of tachycardia for the previous six months. The duration of a spell varied from a few days to as long as three weeks. His strength and endurance were poor. He had noticed shortness of breath on exertion for three months, and afternoon swelling of his feet and ankles for one month. He gave no history of the usual childhood diseases except measles. The only other illness was rather frequent sore throat for the past three months.

Examination revealed a boy 5 feet 7 inches in height, weighing 145 pounds. His face was flushed. The teeth were in good condition. The tonsils were small, slightly injected and contained a few crypts. No pus could be expressed. The thyroid was soft, and uniformly enlarged to a slight degree. The lungs were normal. There was a diffuse heaving impulse of the heart that was visible over an area measuring 7 by 15 cm and extending from the second to the sixth interspaces immediately to the left of the sternum. The left heart border was found to be 13 cm to the left of the mid-sternal line in the sixth interspace, the right border 3 cm to the right of the mid-sternal line in the fifth interspace. The heart rate was 125 and regular. The pulse was weak, but every beat was felt at the wrist. A gallop rhythm was heard over the entire precordium but was loudest 2 cm to the right of the sternum in the fourth interspace. Three distinct impulses were imparted to the hand placed over the heart. No thrill was palpable, and no murmurs were heard. The examination of the abdomen revealed nothing pathological. The reflexes were normal. There was no evidence of edema, cyanosis, or dyspnea.

The blood pressure was 116/96 mm of mercury. Blood counts and hemoglobin estimations were normal. The blood Wassermann was negative. The urine contained albumin two plus, no casts. The basal metabolic rate was plus 15 and plus 8.

[†] Received for publication February 20, 1933.

From the Medical Departments of Rush Medical College of the University of Chicago and the Presbyterian Hospital of Chicago.

Roentgen-ray examination with a seven foot plate showed the greatest transverse diameter of the chest to be 29.6 cm, and of the heart, 20.5 cm. The greatest width of the supracardiac shadow at the level of the aortic knob was 7 cm. The base of the heart measured 16.5 cm. The lungs were normal. The electrocardiograms are shown in figures 1, 2, and 3.

Diagnosis Paroxysmal tachycardia of right ventricular origin, cardiac dilatation and hypertrophy, heart disease of unknown etiology.



FIG 1 Case I (January 26, 1930) Boy, A. D., 16 years old. Rate 125. Paroxysmal tachycardia of right ventricular origin. Note one normal beat in Lead III. In all tracings 1 cm = 1 mv and time interval = 0.4 second. Note: In Lead III, 0.5 cm = 1 mv. This is the only exception.



FIG 2 Case I A. D. (March 14, 1930) Rate 78. Normal rhythm after quinidine.

Etiology There was none obtainable either for the attacks or for the underlying heart disease. There was no history of previous disease, strain, or excesses which could account for the condition.

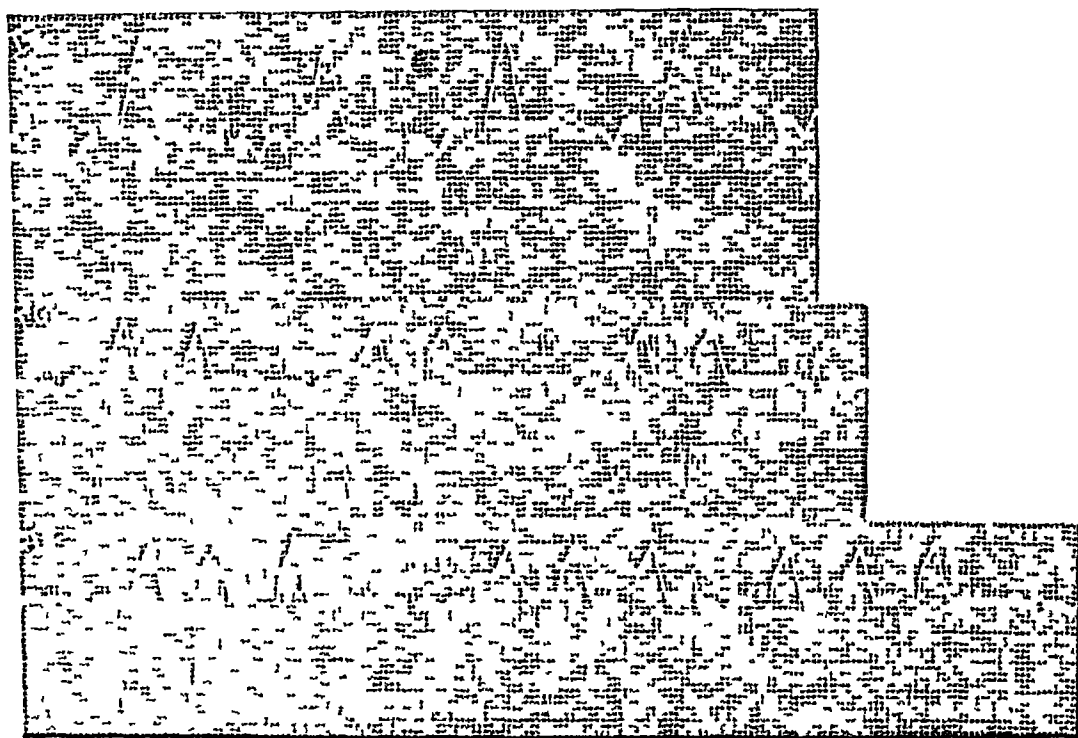


FIG 3 Case I A D All strips are of Lead I Extrasystoles observed throughout subsequent observation

Treatment and Course Vagal and orbital pressure were without effect. The rapid tachycardia was temporarily controlled by quinidine sulphate, given in gradually increased dosage up to 12 grains per day. Examinations, when the rate was normal, showed that the heart had not changed in size. The left border was 11 cm to the left of the mid-sternal line in the sixth interspace, and 3 cm to the right of the mid-sternal line at the fifth interspace. A seven foot roentgen-ray plate taken during normal rate, gave essentially the same measurements as were found during the spell of tachycardia.

The patient continued to take the quinidine, but within a month the spells of tachycardia returned. Quinidine was given up to 42 grains per day, but the rhythm never returned to normal. Runs of right ventricular extrasystoles persisted in spite of digitalis, quinidine, potassium iodide, atropine, strychnine, and morphine. A rapid regular sinus rhythm could be established by exercise, but it would persist for only one or two minutes. At present the patient is at home confined to bed under the care of an outside physician. His condition is very poor, and the prognosis bad.

CASE II

A man, A. L., 59 years of age, entered the Presbyterian Hospital of Chicago, March 31, 1930, because of a recurring biliary fistula. He had had an operation in 1918 for gangrenous gall-bladder with stones. The gall-bladder was not removed. The wound drained for six months and gradually closed. In 1920 the wound broke open and discharged for a few weeks. The fistula then remained closed until one year ago (1929) when it reopened and has discharged ever since. Slight jaundice, chills, and fever developed.

Additional past history disclosed the fact that the patient had had rheumatic fever twice (at 19 and 36 years of age) and had been told that there was some heart involvement each time. Recently he had had some dyspnea and heart consciousness on exertion.

Cholecystectomy was performed April 2, 1930, by Dr. Arthur Dean Bevan who found a common duct obstruction of unknown cause. Convalescence was prolonged due to persistent discharge and to delayed healing of the incision. May 12, 1930, the patient was allowed to be up in a wheel chair for one hour.

On May 13, 1930, the patient on waking stated that he did not feel well and complained of marked tachycardia. Examination revealed a regular pulse rate of 200. No murmurs were heard. The left heart border was 11 cm. to the left of the mid-sternal line in the fifth interspace. The right heart border was substernal. Orbital and vagal pressure were without effect. The electrocardiograms are shown in figures 4 and 5. Note the coronary T-wave in figure 5. There was no history of

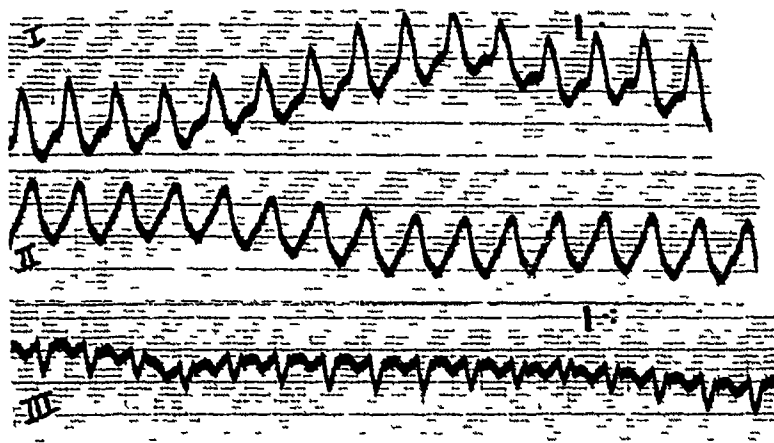


FIG 4 Case II (May 13, 1930) Man, A. L., 59 years old Rate 187 Paroxysmal tachycardia of left ventricular origin

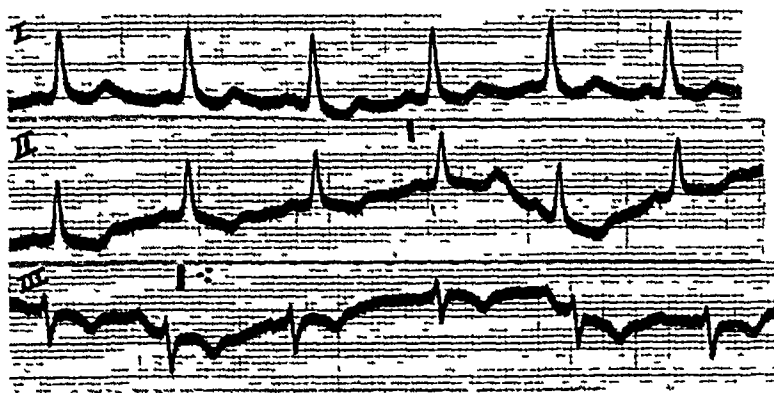


FIG 5 Case II A. L. (May 14, 1930) Rate 83 Normal rhythm, probable coronary T-wave

angina. The attack suddenly ended after about three hours. Extrasystoles persisted for about 30 minutes longer. There were no recurrences in the hospital and the patient was discharged June 14, 1930. Within the following six weeks there were two similar but shorter attacks, each brought on by over-exertion and relieved by rest.

Cardiac Diagnosis Paroxysmal tachycardia of left ventricular origin, history of rheumatic heart disease, probable coronary sclerosis

Etiology The attacks of paroxysmal tachycardia may be attributed to coronary sclerosis. The heart disease is attributed to rheumatic fever. Chronic biliary infection may have been a contributory cause.

Treatment and Subsequent Course The patient was seen frequently and remained free from attacks for four months. In December 1930, he developed acute cardiac decompensation with edema, cyanosis, dyspnea and a total arrhythmia. The electrocardiogram confirmed the diagnosis of auricular fibrillation. At present the fibrillation persists, and the decompensation is slowly responding to digitalis and rest.

CASE III

A man, H. B., 42 years of age, was first seen in the Central Free Dispensary in April 1918. His complaints at that time were palpitation and precordial pain on exertion, joint pains, insomnia and anorexia. The past history revealed measles in childhood, frequent attacks of tonsillitis, chancre in 1905, and gonorrhea in 1910. Four blood Wassermanns were reported to be negative.

Physical examination revealed rather large tonsils. The left border of the heart was 14 cm to the left in the fifth interspace, the right heart border was substernal. There were occasional extrasystoles. A soft murmur was heard over the lower end of the sternum. Lungs, abdomen, and reflexes were normal.

Laboratory examinations showed the hemoglobin 85 per cent, white blood cells 12,000, urine normal, blood Wassermann four plus, blood pressure 130/70 mm of mercury. Roentgen-ray showed an enlarged heart with a tendency towards a mitral configuration.

Diagnosis (April 1918) Syphilis with cardiac hypertrophy and dilatation. Probable syphilitic heart disease.

Treatment Mercury and iodide for one year, then 0.2 gm neosalvarsan intermittently for two years. The patient then disappeared until June 1925, when he returned complaining of epileptiform seizures and precordial pain. The record of the physical examination at that time is not available.

Diagnosis (June 1925) Epileptiform seizures, coronary occlusion, mitral stenosis, auricular fibrillation, syphilis. The electrocardiogram showed a coronary T-wave (see figures 6 and 7).

Treatment Digitalis, neosalvarsan, iodides, and mercury. There was a marked improvement—the blood Wassermann became negative, regular sinus rhythm was restored, the patient's heart was well compensated, and the epileptiform seizures disappeared.

Subsequent Course The patient returned in June 1928, with jaundice and attacks of pain in his gall-bladder region. Cholecystectomy was done by Dr. Harry Oberhelman who found four stones in the gall-bladder. Recovery was rapid. In July 1928, severe left chest pains developed. At this time he gave the first history of spells of tachycardia. These were associated with the attacks of pain in his left chest. He was seen during an attack when the pulse rate was 178 and regular. The heart was considerably enlarged, during this period of tachycardia no murmurs were heard. The electrocardiogram showed a tachycardia of left ventricular origin. Treatment consisted of rest, nitroglycerin, and digitalis. The spells were of rather frequent recurrence for one year. Quinidine was not used. After August 1929, the attacks became less frequent but the pain persisted. Examination at that time revealed aortic regurgitation as well as mitral stenosis. The presence of an Austin Flint murmur is considered but ruled out. The heart had become considerably larger. The left heart border was in the anterior axillary line, the right heart border 3 cm to the right of the right ventricular margin. In January 1930, the heart was compensated and the pa-

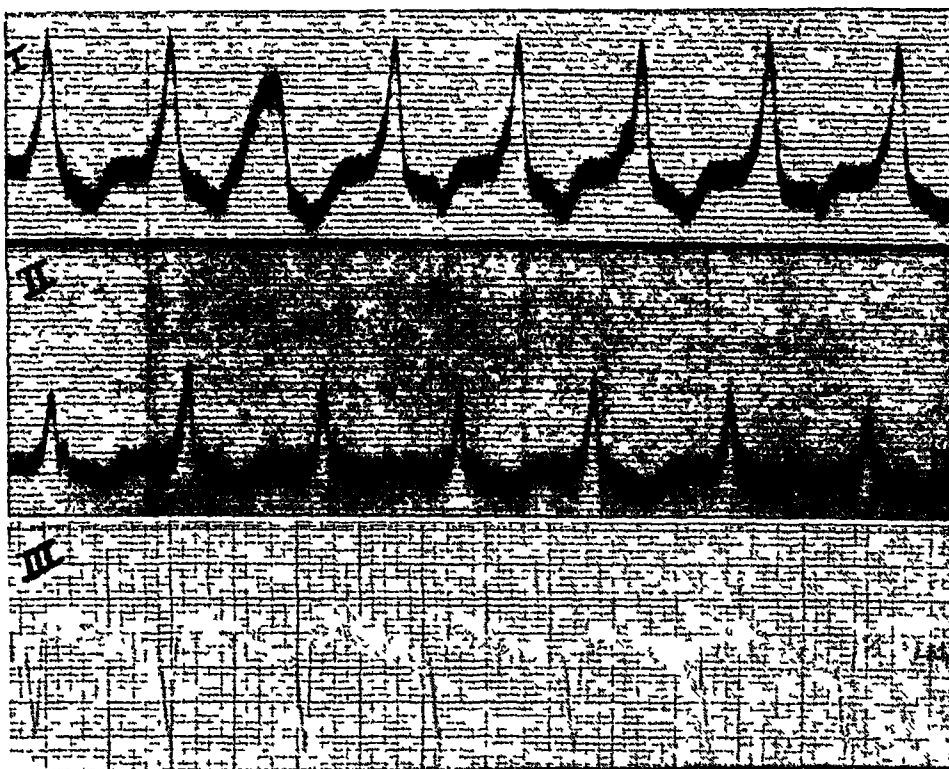


FIG 6 Case III (July 9, 1928) Man, H B, 42 years old Rate 143 Paroxysmal ventricular tachycardia of left ventricular origin Retrograde P-waves in Lead I

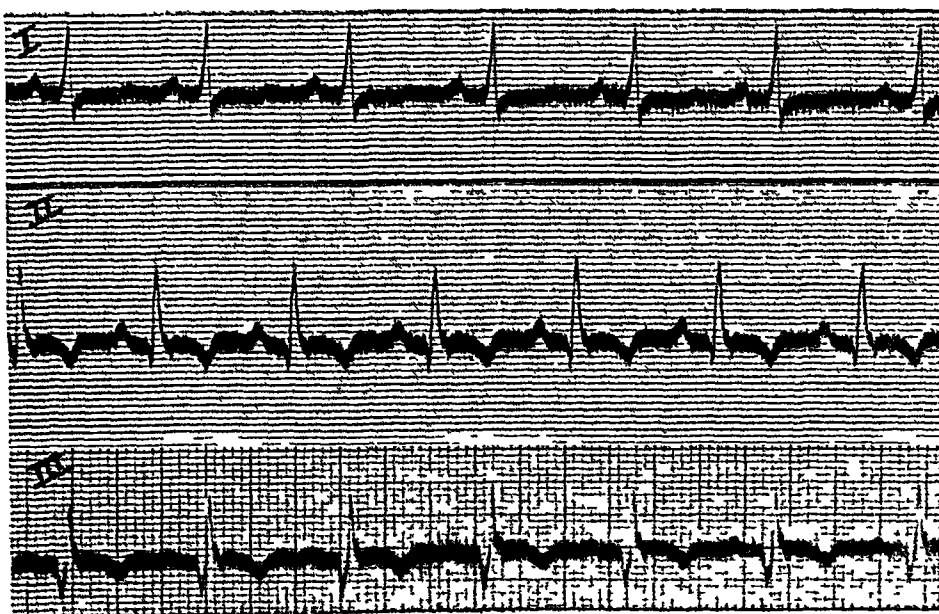


FIG 7 Case III H B (August 25, 1929) Rate 97 Normal rhythm with coronary T-wave

tient was getting along fairly well with 15 drops of tincture of digitalis three times a day, 1/100 grain of nitroglycerin as needed, and 3/4 grain of luminal twice a day

At present the paroxysms of tachycardia still occur, but are infrequent and of short duration, extrasystoles are constantly present

The exciting cause for the attacks of paroxysmal tachycardia would seem to be coronary occlusion, the etiology of the heart disease is syphilis, rheumatism, and chronic tonsillitis

During the past few years, several reviews of this arrhythmia have appeared. These reports are concerned chiefly with only one phase of the sub-

TABLE I
Right Ventricular Type (23 Cases)

Ref No	Our Case No	Age	Sex	Valve Disease	Etiology for Attacks	Etiology for Heart Disease	Degree of Heart Disease	Outcome
1	1	Mid	M	Murmur	Exertion, onset after box fell on leg	Gouty arthritis Influenza	Mod	L
5	5	20	M	—	Diphtheria	Diphtheria	Mild	L
7	11	42	M	—	None	Strept infections	Mod	L
10	19	49	M	Aortic	Coronary occlusion	Syphilis	Mod	L
12	21	39	F	None	None	Rheumatic fever	None	L
13	22	21	F	—	None	None	None	L
						Pneumonia	Mod	L
						Diphtheria		
						Tonsillitis		
17	27	35	F	None	None	Dry pleurisy (In bed 1 yr)	None	L
22	31	60	M	—	None	None	Adv	L
22	35	18	M	Murmur	None	Rheumatic fever	Adv	L
23	38	63	M	Aortic	Digitalis	Arteriosclerosis	Mod	D*
23	10	60	F	Murmur	Digitalis	None	Adv	D
29	18	25	M	—	Focal myocarditis	Abscessed teeth	Adv	D*
					Early coronary arteritis	Infected tonsils		
30	49	53	M	—	Exertion	None	Mod	L
31	58	18	M	—	None	Pneumonia twice	None	L
35	59	?	M	Mitral	Coronary disease	Hypertension	Adv	L
38	62	50	F	—	None	Rheumatism	Mild	L
42	71	53	M	—	Coronary thrombosis	None	Mod	L
44	71	17	?	—	None	None	Mild	L
45	78	51	M	—	Coronary thrombosis	None	Adv	D*
47	80	20	M	None	None	None	None	L
47	81	25	M	None	None	None	None	L
51	88	17	M	—	Undue excitement	None	None	L
52	89	16	M	—	None	None	Adv	L

* Autopsy

ject. No one has tabulated all of the proved cases and analyzed the exciting causes for the onset of the attacks in relation to the underlying heart disease. We have made such a survey and have found some valuable information by

correlating the individual case histories with a classification of the types of this arrhythmia

We have found reference to 149 cases which, with our own, make a total of 152 cases. Of these 152 cases, 56^{5, 7, 9, 31, 45, 53-75, 81} were discarded as unproved because of questionable or absent electrocardiograms or because of insufficient historical data. The data of the remaining 96 cases were studied with reference to age, sex, etiology of the attacks, etiology of the associated heart disease, the degree of heart disease, the type of arrhythmia,

TABLE II
Idio-Ventricular Type (23 Cases)

Ref No	Our Case No	Age	Sex	Valve Disease	Etiology for Attacks	Etiology for Heart Disease	Degree of Heart Disease	Outcome
3	3	45	M	Mitral Aortic Murmur	Coronary disease	None	Adv	D*
4	4	48	M	—	Rheumatism	Rheumatism	Mod	L
5	6	Young	M	—	None	None	None	L
5	7	Young	M	—	Exertion	None	None	L
6	9	50	M	—	Poor blood supply	None	Mod	L
7	10	62	M	—	None	Strept infections	Mod	L
9	15	23	F	Mitral	Terminal digitalis	Rheumatic fever	Adv	D
10	18	53	F	—	Coronary occlusion	None	Adv	D
19	30	52	M	—	Coronary occlusion	Arteriosclerosis	Adv	L
23	37	50	F	Mitral	Digitalis	Hypertension	Adv	L
25	42	46	M	Aortic?	Coronary occlusion	None	Mod	L
26	43	32	M	—	None	Rheumatism	Mod	L
33	55	61	M	—	Coronary disease	Arteriosclerosis	Adv	D
						Asthma		
						Influenza		
33	57	19	M	—	None	None	None	L
39	63	12	M	—	None	None	Mild	L
40	64	71	M	—	Digitalis	Asthmatic bronchitis	Adv	L
					Ouabaine			
41	70	74	M	Murmur	Digitalis	Arteriosclerosis	Adv	D
						Hypertension		
43	72	50	M	—	Digitalis	Arteriosclerosis	Adv	D*
					Coronary thrombosis	Hypertension		
45	75	41	F	—	None	Influenza	Mild	L
50	85	47	M	—	Digitalis	Hypertension	Mod	D*
					Coronary thrombosis			
50	86	54	M	—	Coronary occlusion	Hypertension	Adv	D
					Digitalis?			
79	92	16	F	—	None	None	None	L
81	95	52	M	—	Exertion	Coronary disease	Mild	L
						Arteriosclerosis		

* Autopsy

factors which might influence the type of arrhythmia, the outcome, and the revelations and bearings of autopsy findings. It may be objected that in a few instances the type of arrhythmia was determined from only one lead. These few instances, however, are not enough to make a significant differ-

ence in the results, so we feel justified in adding them to our series. Another criticism might be made regarding the inclusion of the alternating bi-directional type of the arrhythmia. This type is by some regarded as an alternating bundle branch block due to excessive digitalis administration.²⁹ The type is usually considered as ventricular. We include it for this reason, although we do not consider it to be a true paroxysmal ventricular tachycardia.

We are adhering to the old terminology with regard to the type of the arrhythmia. When QRS is upright in Lead I and inverted in Lead III we call this the left ventricular type.

The tabulation of our findings, according to types, follows.

A significant observation is that excessive digitalis administration is held responsible for 35 (36 per cent) out of the total of 96 cases of all types of this arrhythmia. The association is greater in the left ventricular and idio-ventricular types than in the right. We believe this is due to the fact that digitalis makes the left ventricle work harder than the right (due to the

TABLE III
Left Ventricular Type (35 Cases)

Ref No	Our Case No	Age	Sex	Valve Disease	Etiology for Attacks	Etiology for Heart Disease	Degree of Heart Disease	Outcome
2	2	49	M	Murmur	Coronary disease	Syphilis	Mod	L
6	8	21	M	Aortic Mitral	Poor blood supply	Rheumatism Sore throats	Adv	L
7	12	38	M	—	—	Strept infections	Adv	L
8	13	59	M	Mitral	Terminal	Hypertension	Adv	D*
8	14	63	M	Aortitis	—	Syphilis	Adv	L
10	16	53	M	—	Coronary occlusion	Syphilis	Adv	D*
						Hypertension		
10	17	58	M	—	Coronary occlusion	Arteriosclerosis	Adv	D
						Hypertension		
11	20	22	M	—	Exertion	—	None	L
11	23	58	M	—	Quinidine	—	Adv	L
15	24	20	M	—	None	None	Mod	L
15	25	57	M	Aortic	—	Rheumatism	Adv	L
						Pleurisy		
16	26	?	?	—	Quinidine	—	—	L
20	31	49	M	—	—	Teeth	Mod	L
22	35	20	F	—	—	—	Adv	L
22	36	58	F	Mitral	—	Syphilis	Adv	L
						Hyperthyroidism		
25	39	80	F	—	Digitalis	Chronic tonsillitis	Adv	L
26	41	17	F	—	—	—	None	L
27	41	15	F	—	—	—	Adv	L
28	47	71	M	—	Digitalis	Arteriosclerosis	Adv.	D*
					Coronary thrombosis			
52	52	48	M	Mitral	Exertion	Head colds Pharyngitis	Mod	D (Pneumonia)

TABLE III—(Continued)

Ref No	Our Case No	Age	Sex	Valve Disease	Etiology for Attacks	Etiology for Heart Disease	Degree of Heart Disease	Outcome
33	53	52	F	Mitral Tricuspid	Digitalis	Rheumatic fever	Adv	D*
33	54	64	M	—	Digitalis	Arteriosclerosis Asthma	Adv	D
33	56	41	M	—	Nicotine poisoning	Tobacco	Mod	L
36	60	54	M	—	Coronary thrombosis	Rheumatism	Adv	D*
40	65	63	M	Mitral	Coronary disease (?)	—	Adv	L
41	69	39	F	Aortic Mitral	Digitalis	Rheumatic fever	Adv	D*
45	76	53	M	—	Coronary disease	—	Adv	L
45	77	55	M	—	Exertion Coronary thrombosis	Hypertension	Adv	D*
46	79	46	M	Aortitis	Exertion Coronary disease	Syphilis	Adv	D*
48	82	45	F	—	Pressure inf vena cava Megacolon	—	Mild	D*
49	84	73	M	—	Digitalis Coronary occlusion	Arteriosclerosis	Adv	D
52	90	59	M	—	Coronary disease	Rheumatic fever Biliary infection	Adv	L
52	91	42	M	Aortic Mitral	Coronary disease	Syphilis Chronic tonsillitis	Adv	L
80	93	66	F	—	Coronary disease	Coronary disease Arteriosclerosis	Adv	D
81	95	31	M	—	Exertion Excitement	Hypertension Scarlet fever Pneumonia	Mod	D

* Autopsy

fact that the resistance opposed to the complete emptying of the ventricles is greater for the left ventricle than for the right) In the presence of disease, the left ventricle and septum would therefore undergo a disproportionate strain Digitalis intoxication in the presence of advanced heart disease is held accountable for 100 per cent of the cases showing the alternating bi-directional type

No exciting causes could be determined for the attacks in 28 cases In this group the right ventricular type predominates, 12 in number, while there are only nine in the larger group of the left ventricular type This seems significant, especially in view of the association of the right ventricular type with a lower age incidence and a lesser degree of heart damage than in the left Within the groups according to types, 12 cases (52 per cent) of the right ventricular type gave no exciting causes, and only 9 cases (25 per cent) of the left ventricular type failed to be associated with exciting factors for the attack This observation seems to be associated with a better prognosis for the right ventricular type

Coronary disease is associated with the onset of the attacks in 27 cases (28 per cent) The frequency of occurrence is greater in the left than in

TABLE IV
Alternating Bi-directional Type (21 Cases)

Ref No	Our Case No	Age	Sex	Valve Disease	Etiology for Attacks	Etiology for Heart Disease	Degree of Heart Disease	Outcome
18	28	50	F	Aortitis	Digitalis	Syphilis	Adv	D*
18	29	61	F	Mitral	Digitalis	Aneurysm	Adv	D*
21	32	54	F	—	Digitalis	Rheumatic fever	Adv	D
28	45	64	F	—	Digitalis	Hypertension	Adv	D
28	46	44	F	—	Digitalis	None	Adv	D
31	50	77	M	—	Digitalis	Exophthalmic goiter	Adv	D*
31	51	66	M	Aortic	Coronary disease	Arteriosclerosis	Adv	D*
37	61	76	M	—	Digitalis	Syphilis	Adv.	D
					Digitalis	Arteriosclerosis	Adv	D*
					Coronary thrombosis			
41	67	53	F	None	Digitalis	Hypertension	Adv	D*
41	68	42	F	Murmur	Digitalis	Arteriosclerosis	Adv	D
						Hypertension		
43	73	45	M	—	Digitalis	Chronic sore throat	Adv	D
49	83	49	M	Aortic	Digitalis	Syphilis	None	D*
50	87	65	M	Aortic	Digitalis	Syphilis, obesity	Adv	D
41	66	59	M	Aortic	Digitalis	None	Adv	D*
				Mitral				
23	39	80	F	—	Digitalis	Chronic tonsillitis	Adv.	L
28	47	71	M	—	Digitalis	Arteriosclerosis	Adv	D*
					Coronary disease			
41	69	39	F	Aortic	Digitalis	Rheumatic fever	Adv	D*
				Mitral				
41	70	74	M	Murmur	Digitalis	Arteriosclerosis	Adv	D
						Hypertension		
43	72	50	M	—	Digitalis	Arteriosclerosis	Adv	D*
					Coronary thrombosis	Hypertension		
50	85	47	M	—	Digitalis	Hypertension	Mod.	D*
					Coronary thrombosis			
52	96	40	M	—	Digitalis	Rheumatic fever	Adv	L

* Autopsy

the right ventricular type, which conforms to the generally recognized fact that coronary disease involves the left ventricle more often than it does the right ventricle.

Exertion is associated with the onset in 9 cases (9 per cent) Most of these, five cases, were of the left ventricular type This is in contrast to the observation that in athletes the right ventricle hypertrophies This difference may be due to the fact that exertion on the part of an untrained person causes strain on the left ventricle, whereas in long continued effort the strain is on the right ventricle Concomitant coronary disease may have helped determine the type in two of these cases

Upon arranging this information according to groups, the following relationships are shown

TABLE V
Summary of Exciting Causes for the Onset of Attacks

Number of Cases	Exciting Cause	Types			
		Right Ventricular	Idio-Ventricular	Left Ventricular	Alternating Bi-Directional
96 total		23 cases	23 cases	35 cases	21 cases
35 (36%)*	Digitalis	2 (9%)†	6 (26%)†	6 (17%)†	21 (100%)† includes 6 duplicated types
28 (29%)*	None	12 (52%)†	7 (30%)†	9 (26%)†	5 (24%)† includes 3 duplicated types
27 (28%)*	Coronary disease	5 (22%)†	8 (35%)†	13 (37%)†	0
9 (9%)*	Exertion	2 (9%)†	2 (9%)†	5 (14%)†	0
8 (8%)*	Pulmonary disease	3 (13%)†	2 (9%)†	3 (9%)†	0
3 (3%)*	Toxic and infectious	1 (4%)†	1 (4%)†	1 (3%)†	0
3 (3%)*	Nervous	2 (9%)†	0	1 (3%)†	0
2 (2%)*	Quinidine	0	0	2 (5%)†	0

* % refers to total number of cases considered

† % refers to total number of cases considered of this type

Note The correct percentage and relationship of terminal cases could not satisfactorily be determined. Two cases reported by Dieuaide and Davidson⁹ are probably representative of the type to be expected under these circumstances. These included one left ventricular and one idio-ventricular type.

Pulmonary disease is associated with the onset in eight cases. While this group is small it seems worth while to call attention to the fact that within the sub-groups, three or 13 per cent were of the right type, whereas three in the larger group of the left type constitute only 9 per cent, showing a higher incidence in the right type. The strain on the right heart as a result of pulmonary circulation embarrassment may have been a factor in the production of the right ventricular type of the arrhythmia in these cases.

Nervous factors influencing the onset occurred more often in the right type than in the left. Quinidine was associated with the onset in two cases of the left type.

These results differ from those published by Strauss¹⁰ largely because of the recent addition of quite a number of cases to the literature. The most notable differences are the shifting of arteriosclerotic heart disease and coronary disease to first and third places respectively instead of second and fourth. Hypertensive heart disease is displaced from first to fifth place. The percentage of rheumatic heart disease remains the same but moves from third to sixth place. The percentage of syphilitic heart disease is doubled, but its relative position of importance remains the same. The percentage

of undetermined kind of heart disease is greatly increased from 11 per cent to 32 per cent. We have listed (table 7) 13 cases (14 per cent) associated with no demonstrable heart disease, which agrees with Strauss' report of 11 cases or 15 per cent.

TABLE VI
Kinds of Associated Heart Disease with Relation to Type of Arrhythmia

Number of Cases	Kinds of Disease	Types			
		Right Ventricular	Idio-Ventricular	Left Ventricular	Alternating Bi-Directional
96	(163 reported)	23 cases	23 cases	35 cases	21 cases
33 (34%)*†	Arterio-sclerotic	6 (26%)‡	10 (43%)‡	14 (40%)‡	6 (29%)‡ includes 4 duplicate types
31 (32%)*	Not determined	11 (48%)‡	9 (39%)‡	9 (26%)‡	2 (10%)‡
29 (30%)*	Coronary disease	5 (21%)‡	4 (17%)‡	13 (37%)‡	5 (24%)‡ includes 3 duplicate types
20 (21%)*	Toxic and infectious	6 (26%)‡	4 (17%)‡	9 (26%)‡	1 (5%)‡
17 (18%)*	Hypertensive	1 (4%)‡	5 (22%)‡	5 (14%)‡	6 (29%)‡
16 (16%)*	Rheumatic	4 (17%)‡	3 (13%)‡	6 (17%)‡	5 (24%)‡
14 (15%)*	No heart disease	6 (26%)‡	4 (17%)‡	3 (9%)‡	1 (5%)‡
11 (12%)*	Syphilitic	1 (4%)‡	0	6 (17%)‡	4 (18%)‡
2 (2%)*	Thyrototoxic	0	0	1 (3%)‡	1 (5%)‡
1 (1%)*	Obesity	0	0	0	1 (5%)‡

* % refers to the total number of cases considered in this series.

† includes 29 cases of coronary disease listed below

‡ % refers to the total number of cases within the group of this type

In addition, we call attention to the fact that hypertensive, arterio-sclerotic, coronary, and syphilitic heart diseases are associated with a higher percentage of cases of the left ventricular type than of the right. This is expected since in all of these instances the heart damage is usually greatest in the left ventricle. Rheumatic heart disease does not live up to expectations in that the percentages of the left and right ventricular types are equal. We expected to find more of the right ventricular type since mitral disease is more common than aortic disease, and in mitral disease the stress and strain is greatest in the right ventricle. This exception affords an excellent opportunity to apply, to paroxysmal ventricular tachycardia, F. N. Wilson's⁸¹ recent contributions to heart physiology, in which he gives reasons for reversing our present conception of right and left bundle branch block. This is an explanation worthy of serious consideration, and could be readily accepted were it not for the fact that all of the other kinds of heart disease are associated with the types which agree with our present conception of paroxysmal left and right ventricular tachycardia. We will return to this discussion when we consider the autopsy findings in the various types and draw our final conclusions at that time. For the present we will continue our reasoning while accepting the classical terminology and offer as an ex-

planation for this unexpected association the thought that after all, in mitral disease, the disease is on the left side of the heart. Later we shall show that in valvular disease, the type of arrhythmia which occurred was influenced by co-existing disease.

Toxic and infectious diseases of the heart also have an equal percentage of both types.

Attention is called to the fact that in 31 cases, where the kind of heart disease was not determined, there is a higher percentage of the right ventricular type than of the left.

TABLE VII
Degree of Myocardial Damage Associated with Types

Total Number	Degree of Damage	Types			
		Right Ventricular	Idio-Ventricular	Left Ventricular	Alternating Bi-Directional
102 includes 6 duplicates		23 cases	23 cases	35 cases	21 cases
14 (14%)	None	6 (26%)	4 (17%)	3 (9%)	1 (5%)
7 (7%)	Slight	3 (13%)	3 (13%)	1 (3%)	0
20 (20%)	Moderate	7 (30%)	6 (26%)	6 (18%)	1 (5%)
61 (61%)	Advanced	7 (30%)	10 (44%)	25 (71%)	19 (90%)
47 (47%)	Deaths	4 (17%)	8 (33%)	15 (43%)	19 (90%)

The clinical evidence shows that the degree of myocardial damage is greater in the left ventricular type than in the right, and greatest in the alternating bi-directional type. Likewise the percentage of deaths was more in the left ventricular type than in the right, and greatest in the alternating bi-directional type. Attention is called to the fact that of 14 cases, giving no evidence of heart disease, six were of the right ventricular type and only three were of the left type.

TABLE VIII
Average Age and Sex in Relation to Type

	Types				Grand Averages
	Right Ventricular	Idio-Ventricular	Left Ventricular	Alternating Bi-Directional	
Average Age	36 years	42 years	50 years	58 years	46 years
Males	17 (74%)	18 (81%)	25 (73%)	12 (55%)	68 (73%)
Females	5 (22%)	5 (19%)	9 (24%)	9 (45%)	26 (35%)

(In 2 cases sex was not given)

The average age incidence increases as the type differs, being least in the right ventricular type and greater in the left ventricular type. This corresponds to expectations in that degenerative changes take place in the left side of the heart before the right as age increases. The average age is greatest in the alternating bi-directional type.

There is a greater percentage of males than females, in all the types considered together. In the alternating bi-directional type there is an approximately equal distribution of the sexes, whereas in the other three types the same relationship obtains as is present in the group as a whole. This seems to be a factor which would tend to cause one to exclude that type from true cases of paroxysmal ventricular tachycardia.

TABLE IX
Related Functional Pathology

	Types			
	Right Ventricular	Idio-Ventricular	Left Ventricular	Alternating Bi-Directional
Auricular flutter and fibrillation and supraventricular paroxysmal tachycardia	2	0	14	6
Decompensation	5	8	16	13
TOTAL	7 (30%)	8 (38%)	30 (91%)	19 (95%)

It is seen that almost all of the left ventricular and alternating bi-directional types had some functional disturbance whereas only 30 per cent of the right ventricular type showed such disturbance. These figures agree very well with those of Strauss,¹⁹ and further substantiate the evidence that the left ventricular and alternating bi-directional types are associated with more advanced heart disease.

TABLE X
Valvular Disease

		Right Ventricular	Idio-Ventricular	Left Ventricular	Alternating Bi-Directional
9	Mitral	23 cases	23 cases	35 cases	21 cases
10	Aortic	1 (4%)	2 (9%)	5 (14%)	1 (5%)
6	Aortic and mitral	2 (9%)	1 (4%)	3 (9%)	4 (20%)
		0	1 (4%)	3 (9%)	2 (10%)

It is logical to expect that uncomplicated valvular disease would show a definite relationship to the type of arrhythmia produced. Unfortunately there are only a very few uncomplicated cases of valvular disease in this group. The one case (No. 59) of mitral disease which showed the right ventricular type also had advanced hypertensive heart disease and coronary occlusion. Apparently these complicating conditions did not influence the type of the arrhythmia. Of the five cases with mitral disease which showed the left ventricular type, four (Nos. 13, 36, 52, 65) had complicating factors, such as hypertension, syphilis, coronary disease, exertion, and terminal effects which overcame the influence of the mitral disease and caused the left ventricular type of the arrhythmia. The fifth case (No. 53) had no complicating factors which can account for the left ventricular type.

In the two cases of aortic disease which showed the right ventricular type, no explanation is apparent for the discrepancy. Of the three cases of aortic disease, which showed the left ventricular type, two (Nos 14 and 79) had complicating factors which might have accounted for the type, but one (No 25) did not.

Of the three cases with combined aortic and mitral disease, two (Nos 80 and 69) had no complications which might influence the type, while the other (No 91) did. Since the complications present in this case would tend to produce the left ventricular type, it may be that which accounts for this instance acting as expected.

In summary it might be said that the influence of these kinds of valvular disease on the type of the accompanying arrhythmia, cannot be determined because of the paucity of uncomplicated cases. Of the 19 cases showing mitral or aortic disease only four were uncomplicated, which number is obviously too small to consider. It must be mentioned, however, that in these four instances there were three which showed the opposite type to that which was expected, while only one (No 25) was associated with the expected type.

Our conclusions in regard to the influence of valvular disease on this type of arrhythmia are that the strain imparted to the ventricle does not damage that ventricle sufficiently to set up the mechanism involved in this arrhythmia. Instead, it is merely an added factor when some other disease involves the same ventricle, or a less important factor when more serious disease involves the opposite ventricle.

The available autopsy material shows no case of the right ventricular type with marked disease of the right ventricle. One case (No 48) showed focal myocarditis worse in the left ventricle, and one case (No 78) with infarction of the posterior wall of the left ventricle.

All three cases of the idio-ventricular type showed infarction, No 3 in the septum, No 72 in the posterior and lateral walls of the left ventricle, and No 85 had a healed infarct in the tip of the left ventricle. Its size is not given.

Eight cases of the left ventricular type were autopsied. Two cases (Nos 16 and 79) with possibly a third (No 47) had thrombosis, necrosis, and ecchymotic spots along the left descending coronary artery, respectively, which altered the anterior wall of the left ventricle. Case No 47 is not definite in this regard. Two cases (Nos 60 and 77) had definite involvement of the apex, while three cases (Nos 13, 69 and 82) showed no definite involvement of either ventricle. Four of the eight cases, therefore, showed definite pathology in the left ventricle which might have been a factor in determining the left ventricular type of this arrhythmia in these instances. It should be noted that all of these instances involved the apex or anterior wall of the left ventricle.

Of 11 autopsies in cases of the alternating bi-directional type, three showed thrombosis (Nos 66 and 72) or infarction (No 85). Two of

AUTOPSY FINDINGS

Right Ventricular	Idio-Ventricular	Left Ventricular	Alternating Bi-Directional
<p><i>Ref 29, Case 38</i> Heart weight 320 grams Coronary hypertrophy and dilatation Moderate sclerosis of the aorta and coronaries Aortic cusps thickened Right atricle dilated</p>	<p><i>Ref 3, Case 3</i> Most marked changes in the interventricular septum Dilatation of right auricle and ventricle Thickening of aortic and mitral valves</p>	<p><i>Ref 10, Case 16</i> Thrombosis of the anterior descending branch of the left coronary artery Thickening of the walls of the circumflex branch of the left coronary artery</p>	<p><i>Ref 18, Case 28</i> Cardiac hypertrophy Syphilitic aortitis Aortic aneurysm No coronary thrombosis</p>
<p><i>Ref 20, Case 48</i> Focal myocarditis (worse in left ventricle and both auricles) Early coronary endarteritis Acute and chronic myocarditis</p>	<p><i>Ref 13, Case 72</i> (Later changed to Alt Bi-D type) Heart weight 545 grams Circumflex branch of the left coronary artery showed a narrow lumen The descending branch of the left coronary was markedly narrowed and obliterated by a fresh thrombus Necrosis of the lower half of the posterior and lateral walls of the left ventricle</p>	<p><i>Ref 28, Case 47</i> (Later changed to Alt Bi-D type) Heart weight 600 grams Echymotic spots along the left descending coronary Sub-epicardial hemorrhage Generalized arteriosclerosis Cardiac hypertrophy and dilatation</p>	<p><i>Ref 18, Case 29</i> Mitral endocarditis Hypertrophy of right ventricle Hypertrophy and dilatation of the right auricle No coronary thrombosis</p>
<p><i>Ref 15 Case 78</i> Occlusion of the circumflex branch of the left coronary with infarction of the posterior wall of the left ventricle</p>	<p><i>Ref 50, Case 85</i> (Later changed to Alt Bi-D type) Heart weight 950 grams Healed infarct at tip of left ventricle</p>	<p><i>Ref 36, Case 60</i> Fibrous myocarditis and endocarditis Thrombosis of a branch of the left descending coronary artery Coronary sclerosis Aneurysm at apex of left ventricle</p>	<p><i>Ref 31, Case 50</i> Coronary sclerosis Many ischemic myocardial lesions</p>
		<p><i>Ref 41, Case 69</i> (Later changed to Alt Bi-D type) Heart weight 630 grams Widespread acute inflammatory process in and about walls of smaller coronary arteries</p>	<p><i>Ref 37, Case 61</i> Heart weight 520 grams General arteriosclerosis Lumen of the anterior descending branch of the left coronary, two-thirds occluded</p>
		<p><i>Ref 41, Case 66</i> Heart weight 850 grams Healed mitral endocarditis Healed and calcified aortic endocarditis with advanced stenosis Diffuse fibrosis of the myocardium Organizing mural thrombi in the ventricles</p>	

AUTOPSY FINDINGS (Continued)

Right Ventricular	Idio-Ventricular	Left Ventricular	Alternating Bi-Directional
		<i>Ref 45, Case 77</i> Thrombosis of left coronary artery with a large infarct involving the tip of the left ventricle which had ruptured	<i>Ref 41, Case 66</i> Organizing pericarditis Cardiac hypertrophy and dilatation Anasarca Pulmonary infarcts
		<i>Ref 46, Case 79</i> Heart weight 400 grams Syphilitic aortitis with insufficiency Partial occlusion of left coronary Myocardial necrosis of left ventricle	<i>Ref 41, Case 67</i> Heart weight 659 grams Left bundle branch showed degenerative changes
		<i>Ref 48, Case 82</i> Megacolon Heart slightly enlarged Valves normal	<i>Ref 49, Case 83</i> Dilated aorta with two dilatations Adherent pericardium Normal myocardium, endocardium and coronary arteries
		<i>Ref 8, Case 13</i> Heart weight 740 grams Slight coronary sclerosis	<i>Ref 28, Case 47</i> See under left ventricular type No infarction
			<i>Ref 41, Case 69</i> See under left ventricular type No infarction
			<i>Ref 43, Case 72</i> Thrombosis present See under idio-ventricular type
			<i>Ref 50, Case 85</i> Infarction present See under idio-ventricular type

these cases had a preceding idio-ventricular type of paroxysmal ventricular tachycardia

In summary we find that there seems to be easily demonstrable autopsy evidence, showing disease of the left ventricle which could account for the left ventricular type of this arrhythmia. This was certain in four out of eight autopsies. One out of three cases gave understandable evidence of disease in the septum which could account for the idio-ventricular type. The evidence from autopsies on cases of the right ventricular type is contradictory, indicating in two out of three cases more disease in the left ventricle. We would emphasize the fact that one of these two cases had infarction of the posterior wall of the left ventricle, in contradistinction to the tendency for involvement of the apex or anterior wall of the left ventricle in the left ventricular type. The low incidence of infarction, three out of 11 autopsies, in the alternating bi-directional type is also emphasized at this time.

THE RELATIONSHIP OF ETIOLOGY TO THE MECHANISM OF THE VARIOUS TYPES OF THIS ARRHYTHMIA

The mechanism involved in the production of this arrhythmia has been explained many times. Little, however, has been written which is based upon such a study as this or which takes into account the altered concept of the relationship between ventricular activity and the electrocardiogram which has resulted from the work of Barker, Macleod, and Alexander⁸¹. The simple statement, that in most of the cases herein studied there was agreement between the type of the arrhythmia and the site of action of the offending heart disease, by no means ends the discussion about paroxysmal ventricular tachycardia. The problem regarding the site of origin of the arrhythmia still remains unsolved. The evidence here presented gives, however, a firm basis for saying that in most instances the site of the new pacemaker in this arrhythmia is in the left ventricle in those cases considered to be of the left ventricular type, according to classical terminology. As previously stated, this need not be considered contradictory to the conclusions of Wilson with reference to bundle branch block.

Primarily we should like, for several reasons, to remove the alternating bi-directional type from the category under discussion. First of all, because the QRS complexes in this arrhythmia are not in every case prolonged as they are in the true ventricular tachycardias where a duration of nearly 0.16 second is almost the rule. Secondly, because while the age incidence and the death rate are highest in this group, marked destruction of the integrity of the ventricular musculature is absent in 75 per cent of the cases and this would suggest that the Purkinje system is more implicated than is the ventricular musculature. Furthermore, this type of the arrhythmia is attributed to excess digitalis administration in nearly 100 per cent of the published cases. This tends to indicate that digitalis is probably solely responsible for the condition since the degree of myocardial damage found in the supposed cases of this type did not seem sufficient alone to have caused

the arrhythmia, and in the autopsied cases of the other types of this arrhythmia when no greater degree of myocardial damage was found there were likewise grounds to attribute the condition to excess digitalis. Its occurrence in females in the same proportion as in males may also be evidence that the myocardium itself is not the site of the disturbance, because the male is known to be more active than the female and there would be a preponderance of cases among the males, in accordance with the incidence among the other types, if the ventricular musculature were at fault.

With regard to the mechanism of the alternating bi-directional type, we agree, and have witnessed in one unreported case, that it is induced by digitalis administration in the presence of a greatly enlarged heart. We cannot agree to the theory of an alternating block of a bundle branch because the QRS complexes are within the conventional 0.1 second duration. Frequently alternating QRS complexes are of longer duration than others, and this forms the basis for our conception of the arrhythmia. We believe that it is likely to be due to alternating incomplete block of one bundle branch and that it is probably very similar to, if not identical with, the mechanism of coupled beats so often seen in connection with excess digitalis administration. The frequent occurrence under digitalis administration of sinus node, A-V node and His bundle block, complete or incomplete, is ample evidence of the predilection of digitalis for blocking parts of the Purkinje system, and these conditions frequently precede or accompany this type of arrhythmia.

We cannot deny the association of disease of the left ventricle with the left ventricular (classical) type of this arrhythmia. This conforms to the reasonable assumption that the diseased left ventricle would be more likely to set up the arrhythmia than the less diseased right ventricle. We believe that the mechanism is probably due to an irritative lesion of some division of the left branch of the His bundle as suggested by Froment,⁸⁶ and probably as a result of extension from the adjacent ventricular musculature.

Likewise it cannot be denied that the right ventricular (classical) type showed a distinct lack of association with those diseases which have been shown to be present in connection with the left type. There was a slight tendency to an association with pulmonary diseases in some instances, especially with pneumonia, and this must be considered. The outstanding features of this type are the lower age incidence, the presence in most cases of only mild heart disease or none, and the fact that this type has the lowest death rate.

It must be said, therefore, that the etiology for the right ventricular (classical) type is not clear. Further evidence must be produced, and more cases must be studied in this manner, before such associations can be made.

Theorizing with regard to this type is irresistible. In the one case (No. 78) in which infarction was found it involved the posterior basal wall of the left ventricle, while in the left type, the four cases of infarction all involved the apex or anterior wall of the left ventricle. We cannot refrain

from pointing out a possible connection between arrhythmias of the right ventricular type having QRS_1 inverted and T_1 upright and QRS_2 upright and T_2 inverted, and cases of coronary occlusion of the posterior basal portion of the left ventricle which have T_{2-3} inverted as observed by Barnes and Whitten.⁷⁷ It may be that, when this region is infarcted and the Purkinje system is irritated sufficiently to set up this arrhythmia, the T-waves take direction as reported and the QRS complexes are oppositely directed which would give us our picture of paroxysmal tachycardia of right ventricular origin (classical)

With regard to the influence of a recent tendency to revise our terminology, especially in connection with ventricular extrasystoles⁸³ and bundle branch block,⁸⁷ we would say that at this time our observations with regard to the left ventricular type (classical) do not support such a revision as applied to paroxysmal ventricular tachycardia

However, we would point out that such observations as were made by Barker, Macleod, and Alexander,⁸³ Marvin and Oughterson,⁸¹ and Lundy and Bacon,⁸⁵ are not yet complete. Neither have they been confirmed in every detail. Until this is done we shall have to hold in abeyance our judgment in this matter. We would emphasize, however, that it seems to be destined that we will have to revise the classical nomenclature of paroxysmal ventricular tachycardia, because proof is gradually accumulating that ventricular extrasystoles, from either right or left ventricle, have different configurations according to the site of origin within the respective ventricles

SUMMARY

1 We agree that the basic mechanism underlying this arrhythmia is laid down by disease of the ventricular musculature

2 Considerable evidence is advanced which tends to show a relationship of different kinds of heart disease to different types of this arrhythmia

3 The mechanism involved in determining the type of this arrhythmia is considered to be heart disease which involves one ventricle more than the other, or a region of one ventricle more than the remainder of the same ventricle, and thereby influences the type according to the ventricle, or its part which has the greater involvement. The suggestion is made that the two types (right and left) may arise from the same ventricle (the left) in different locations. Changed cardiodynamic balance between the two ventricles may be a factor in determining the type by exerting more wear on one ventricle.

4 Basic causes of this arrhythmia are listed in table 6

5 Basic causes of the arrhythmia are related to the types as follows

a Arteriosclerotic, hypertensive, and syphilitic heart diseases are associated in the highest percentage of instances with the left ventricular type

b In coronary thrombosis the type is influenced by the location of the infarct.

- c* Pulmonary disease, especially pneumonia, was of higher incidence in the right ventricular type
- d* The effect of valvular disease could not be determined
- c* Age exerted an influence as described
- f* The stage of heart disease was associated in a definite manner
- g* Males develop this arrhythmia twice as often as females
- h* Undetermined heart disease was found in 32 per cent of the cases and had a greater relationship to the right ventricular type
- i* No demonstrable heart disease was present in 14 per cent of the cases, most commonly in the right ventricular type
- 6 The exciting causes of this arrhythmia are listed in table 5
- 7 Exciting causes of the arrhythmia are related to the types as follows
 - a* Excess digitalis administration was associated with 100 per cent of the alternating bi-directional type. It was associated with the left type twice as often as with the right
 - b* Coronary thrombosis influenced the type according to its location as described
 - c* Excitation was most often associated with the left ventricular type
 - d* Decompensation and auricular fibrillation and flutter were associated most often with the left type
 - e* Nervous and emotional factors are more common in the right ventricular type
- 8 Paroxysmal ventricular tachycardia is seen most frequently in the fourth and fifth decades. The youngest patient was aged 16
- 9 The arrhythmia is more common in males (73 per cent) than in females (35 per cent)
- 10 The prognosis is utterly grave in the alternating bi-directional type and only relatively less so in the left ventricular, idio-ventricular, and right ventricular in the order named. In the absence of demonstrable heart disease the prognosis is best in the right ventricular type. Death occurred during the period of observation in 47 cases (47 per cent of the 96 cases whose histories were studied)

11 Reasons are given for not completely ignoring the application of the newer terminology to this arrhythmia

12 Reasons are given for excluding the alternating bi-directional type, from true cases of paroxysmal ventricular tachycardia. The mechanism of this type is discussed

BIBLIOGRAPHY

- 1 LEWIS, T. Single and successive extrasystoles, *Lancet*, 1909, i, 382-385
- 2 HART, T. S. Paroxysmal tachycardia, *Heart*, 1912-1913, iv, 128-134
- 3 BUTTERFIELD, H. G., and HUNT, G. H. Observations on paroxysmal tachycardia, *Quart. Jr. Med.*, 1914, vii, 209-220
- 4 COHN, A. E., and FRASER, F. R. Paroxysmal tachycardia and the effect of stimulation of the vagus nerves by pressure, *Heart*, 1913-1914, v, 93-104
- 5 HUMF, W. E. Paroxysmal tachycardia, *Quart. Jr. Med.*, 1918, xi, 131
- 6 VAUGHAN, W. T. A study of paroxysmal tachycardia, with especial reference to tachycardia of ventricular origin, *Arch. Int. Med.*, 1918, xxi, 381-398

- 7 WILLIUS, F A Paroxysmal tachycardia, *Boston Med and Surg Jr*, 1918, clxxviii, 40
- 8 GALLAVARDIN, L Tachycardie ventriculaire terminale succédant à une arythmie complète et compliquée de troubles rythmiques divers, *Arch d mal du coeur*, 1920, xiii, 207-209
- 9 DIEUAIDF, F R, and DAVIDSON, E C Terminal cardiac arrhythmias, *Arch Int Med*, 1921, xxviii, 663
- 10 ROBINSON, G C, and HERRMANN, G R Paroxysmal tachycardia of ventricular origin, and its relation to coronary occlusion, *Heart*, 1921, viii, 59
- 11 BARCROFT, J, BOCK, A V, and ROUGHTON, F J Circulation and respiration in paroxysmal tachycardia, *Heart*, 1921, ix, 7-13
- 12 SCOTT, R W Observations on a case of ventricular tachycardia with retrograde conduction, *Heart*, 1921-1922, ix, 29-309
- 13 MARVIN, H M, and WHITE, P D Paroxysms of tachycardia, *Arch Int Med*, 1922, xxix, 403-417
- 14 LEVY, R L Clinical studies of quinidine, alterations in cardiac mechanism after administration of quinidine to patients with auricular fibrillation with consideration of certain toxic effects of drug, *Arch Int Med*, 1922, xxx, 451-477
- 15 SINGER, R, and WINTERBERG, H Chinin als Herz- und Gefassmittel, *Wien Arch f inn Med*, 1922, iii, 329-364
- 16 LEVY, R L Some results of quinidine in auricular fibrillation, *N Y State Jr Med*, 1922, xxii, 276-280
- 17 GALLAVARDIN, L Extrasystolie ventriculaire a paroxysmes tachycardiques prolongés, *Arch d mal du coeur*, 1922, xv, 298-306
- 18 SCHWENSEN, C Ventricular tachycardia as a result of administration of digitalis, *Heart*, 1922, ix, 199-205
- 19 MARVIN, H M Unusual example of paroxysmal tachycardia with gradual slowing of rate, *Heart*, 1923, xx, 279-287
- 20 WILLIUS, F A Paroxysmal tachycardia with multiple foci of stimulus production, *Ann Clin Med*, 1924-1925, iii, 537-543
- 21 FELBERDAU, D Paroxysmal ventricular tachycardia, *Am Jr Med Sci*, 1923, clxvi, 211-222
- 22 WOLFFERTH, C C, and McMILLAN, T M Paroxysmal ventricular tachycardia, *Arch Int Med*, 1923, xxxi, 184-199
- 23 REID, W D Ventricular ectopic tachycardia complicating digitalis therapy, *Arch Int Med*, 1924, xxxiii, 23-34
- 24 BARKER, P S Ventricular tachycardia during attack of paroxysmal auricular tachycardia, *Heart*, 1924, xi, 67-69
- 25 PORTER, W B Paroxysmal ventricular tachycardia, report of a case lasting 153 hours with recovery, *Am Jr Med Sci*, 1924, clxvii, 821-827
- 26 DILLARD, F R Paroxysmal ventricular tachycardia, *Bull Johns Hopkins Hosp*, 1924, xxxi, 229-232
- 27 CASTELLANO, I Paroxysmal ventricular tachycardia with different rhythms, *Arch d mal du coeur*, 1925, xviii, 301-304
- 28 LITTON, D Clinical studies of digitalis, advanced toxic rhythms, *Arch Int Med*, 1925, xxxv, 87-99
- 29 MAYOR, R H, and WAHR, H R Paroxysmal tachycardia associated with focal myocardium, *Jr Am Med Assoc*, 1926, lxxvi, 1125-1126
- 30 ALLEN, G A Paroxysmal tachycardia of ventricular origin with Stokes-Adams syndrome, with retrograde conduction with partial heart block, *Glasgow Med Jr*, 1926, cv, 440-447
- 31 GALLAVARDIN, L Terminal ventricular tachycardia, alternating or multiform complete, its relation with severe form of ventricular extrasystoles, *Arch d mal du coeur*, 1926, xix, 153-157
- 32 LEVY, R L, and SINGER, R Ventricular tachycardia and auricular fibrillation, *N Y State Jr Med*, 1926, xxvi, 413-420

- 33 GILCHRIST, A R Paroxysmal ventricular tachycardia, *Am Heart Jr*, 1926, i, 546-563
- 34 JONES, T D, and WHITE, P D Paroxysmal ventricular tachycardia, *Am Heart Jr*, 1926, ii, 139-143
- 35 BARRIER, C W Use of quinidine in treatment of ectopic rhythm, *Jr Am Med Assoc*, 1927, LXXIX, 742-745
- 36 FISCHER, R Über unregelmässige ventrikuläre Tachykardie, *Wien Arch f inn Med*, 1927, xiv, 405-428
- 37 SMITH, W C Ventricular tachycardia showing bi-directional electrocardiograms, associated with digitalis therapy, *Am Heart Jr*, 1928, iii, 723-732
- 38 SCHLIEPHAKE, E, and GRAUBNER, W Ventrikuläre paroxysmale Tachykardie mit Salvenbildung, *Deutsch Arch f klin Med*, 1928, clviii, 231-237
- 39 MOORE, H Paroxysmal ventricular tachycardia, *Irish Jr Med Sci*, 1928, 754-759
- 40 ORSI, A, and VILLA, L Sur l'anarchie ventriculaire, *Arch d mal du coeur*, 1928, xxi, 353-368
- 41 MARVIN, H M Paroxysmal ventricular tachycardia with alternating complexes due to digitalis intoxication, *Am Heart Jr*, 1928, iv, 21-52
- 42 LEVINE, S A, and STEVENS, W B Therapeutic value of quinidine in coronary thrombosis complicated by ventricular tachycardia, *Am Heart Jr*, 1928, iii, 253-259
- 43 PALMER, R S, and WHITE, P D Paroxysmal ventricular tachycardia with rhythmic alternation in direction of ventricular complexes in electrocardiogram, report of two cases and review of literature, *Am Heart Jr*, 1928, iii, 454-471
- 44 GALLAVARDIN, L, and VEIL, P Extrasystolie ventriculaire avec salves tachycardiques et accidents vertigineux, *Arch d mal du coeur*, 1929, xxii, 25-29
- 45 LEVINE, S A, and FULTON, M N Effect of quinidine sulphate on ventricular tachycardia, clinical observations, *Jr Am Med Assoc*, 1929, xcii, 1162-1168
- 46 ROBINSON, G C Case of coronary occlusion associated with ventricular paroxysmal tachycardia, *Med Clin N Am*, 1929, xii, 1435-1442
- 47 GALLAVARDIN, L, and VEIL, P Deux nouveaux cas d'extrasystolie ventriculaire avec salves tachycardiques, *Arch d mal du coeur*, 1929, xxii, 738-741
- 48 STARLING, H J Case of megacolon of many years' duration with unusual attacks of paroxysmal tachycardia, *Lancet*, 1930, ii, 1013-1014
- 49 STRAUSS, M B Paroxysmal ventricular tachycardia, *Am Jr Med Sci*, 1930, clxxix, 337-345
- 50 SCHWAB, E H Observations on etiology and treatment of paroxysmal ventricular tachycardia, *Am Heart Jr*, 1931, v, 404-415
- 51 ANDERSEN, M C Paroxysmal ventricular tachycardia, report of case, *Am Jr Med Sci*, 1931, clxxxi, 369-378
- 52 Case reports of this paper
- 53 BARKER, L F Syncopal attacks with history of tachycardia in attacks (question of paroxysmal flutter, fibrillation, or paroxysmal tachycardia) in patient who has had fever with leukocytosis and has shown ectopic beats and intraventricular block in electrocardiograms, *Internat Clin*, 1930, iii, 47-54
- 54 BARNES, A R Cerebral manifestations of paroxysmal tachycardia, *Am Jr Med Sci*, 1926, clxvi, 489-495
- 55 BISHOP, L F Early signs of fibrillation of ventricle as shown by occurrence in electrocardiogram of periods of ventricular tachycardia, *Ann Med*, 1920, i, 58
- 56 BOUVERET, L De la tachycardie essentielle paroxystique, *Rev de med*, 1889, ix, 753, 837
- 57 COHN, A E The present status of the electrocardiographic method in clinical medicine, *Am Jr Med Sci*, 1916, cli, 529-549
- 58 GFRAUDEL, E Études sur la tachycardie paroxystique, tachyventriculie et tachyatrics jumelées, *Arch d mal du coeur*, 1928, xvi, 452-471
- 59 GOLD, H Action of digitalis in presence of coronary obstruction, *Arch Int Med*, 1925, xxxv, 482-491
- 60 HEWLETT, A W Case showing rapid ventricular rhythm with periods of auriculo-ventricular dissociation, *Heart*, 1923, v, 9-19

- 61 HOWARD, T Double tachycardia, coexistent auricular and ventricular tachycardia due to digitalis, *Am Jr Med Sci*, 1927, cxcviii, 165-168
- 62 LEA, E C Auricular fibrillation associated with a high degree of A-V block and paroxysmal tachycardia, *Quart Jr Med*, 1911-1912, v, 388-400
- 63 LEVINE, S A Clinical recognition of paroxysmal ventricular tachycardia, *Am Heart Jr*, 1927, iii, 177-179
- 64 LEVINE, S A Clinical recognition of various types of rapid heart action, *Boston Med and Surg Jr*, 1921, cxcxiv, 53
- 65 OTTO, H L Action of epinephrine upon cardiac rhythm, *Jr Lab and Clin Med*, 1927, xiii, 70-75
- 66 PALFREY, F W Paroxysmal tachycardia confined to the ventricles or to the auricles with illustrative cases, *Med and Surg Rep Boston City Hosp*, 1913, xvi, 182-189
- 67 PALMER, R S, and WHITE, P D Clinical significance of aberrant ventricular response to auricular premature beats and paroxysmal auricular tachycardia, *Am Heart Jr*, 1928, iv, 153-160
- 68 REID, W D Toxic effects of digitalis, *Jr Am Med Assoc*, 1923, lxxxi, 435-439
- 69 ROBINSON, G C, and BRIDGER, J F Ventricular fibrillation in man with cardiac recovery, *Arch Int Med*, 1917, xv, 725-738
- 70 SHOOKHOFF, C Tachycardias, *Med Clin N Am*, 1928, xi, 941-959
- 71 SMITH, F M Quinidine in cardiac irregularities, *Jr Am Med Assoc*, 1922, lxxviii, 877-880
- 72 STRONG, G F, and LEVINE, S A Irregularity of ventricular rate in paroxysmal ventricular tachycardia, *Heart*, 1923, x, 125-131
- 73 WHITE, F C Premature contractions of heart, review of 100 cases, *U S Naval Med Bull*, 1927, xxv, 567-573
- 74 WILLIS, I A and BARNES, A R Paroxysmal tachycardia with special reference to prognosis *Boston Med and Surg Jr*, 1924, cxci, 666-670
- 75 WILLIS, I A Paroxysmal acceleration of heart rate, *Am Heart Jr*, 1927, iii, 230-242
- 76 BARKER, P S, MACFARLANE, A G, and others Excitatory process observed in exposed human heart *Trans Assoc Am Phys*, 1929, xlv, 125-133
- 77 BARNES, A R and WHITNEY, M B Study of R-T interval in myocardial infarction, *Am Heart Jr*, 1929, v, 142-171
- 78 BRAMWELL, C, and FILLS, R Some observations on the circulatory mechanism in marathon runners, *Quart Jr Med*, 1911-1912, v, 388
- 79 McMILLAN, I M, and BEHET, S Ventricular paroxysmal tachycardia, report of case in pregnant girl of 16 years with apparently normal heart, *Am Heart Jr*, 1931, vii, 70-78
- 80 SCHWARTZ, S P Transient ventricular fibrillation, study of electrocardiograms obtained from patient with auriculo-ventricular dissociation and recurrent syncopal attacks *Arch Int Med*, 1932, cxlii, 282-302
- 81 WILSON, F N, WISHART, S W, MACFARLANE, A G, and BARKER, P S Clinical type of paroxysmal tachycardia of ventricular origin in which paroxysms are induced by exercise, *Am Heart Jr*, 1932, viii, 155-169
- 82 HOWARD, T Ventricular tachycardia with alternating complexes, *Am Heart Jr*, 1932, viii, 255-257
- 83 BARKER, P S, MACFARLANE, A G, and ALEXANDER, J Excitatory process observed in exposed human heart *Am Heart Jr*, 1930, v, 720-742
- 84 HOWARD, T, and ORLANDO, A W Form of premature beats resulting from direct stimulation of human ventricle, *Am Heart Jr*, 1932, viii, 471-476
- 85 BARKER, P S, and MACFARLANE, A G Ventricular extrasystoles from the exposed human heart *Arch Int Med*, 1933, lxi, 96-102
- 86 BARKER, P S, and MACFARLANE, A G Extrasystolic ventricular beats, 1932 Masson et Cie, Paris
- 87 BARKER, P S, and MACFARLANE, A G Interpretation of initial deflection of ventricular extrasystole, *Am Heart Jr*, 1931, vi, 637-644

FATAL TULAREMIA

REVIEW OF AUTOPSIED CASES WITH REPORT OF A FATAL CASE*

By LEWIS P GUNDRY, M D , and C GARDNER WARNER, M D ,
Baltimore, Maryland

THE RECOGNITION of tularemia as a disease entity is relatively recent. The discovery of the causative organism in 1911 by McCoy, and the studies made by Francis and others, have served to establish the disease on a firm scientific basis. Three hundred and twenty-three case reports were studied by Francis¹ in 1927 and the four clinical types of the disease noted. The mode of infection, clinical signs and symptoms, and mortality rate were well understood at that time. A study of the human pathology of the disease, however, is somewhat more recent. From 1924, when the first autopsied case was reported by Verbrycke,² to the present, there has been only a limited amount of human autopsy material available. Verbrycke² and Francis and Callender³ first described the microscopic changes in the lesions in man. Goodpasture and House⁴ reported the histopathologic changes in the primary lesion. Permar and MacLachlan,⁵ Blackford,⁶ Foulger⁷ and others have given an accurate description of the pathological changes in the lungs. Foulger, Glazer and Foshay⁷ described for the first time lesions on the peritoneum. More recently, meningeal and cerebral lesions due to *B. tularensis* have been described by Bryant and Hirsch,⁸ and Hartman.⁹ While it is probable that the last word has not yet been said as regards the pathology of tularemia in man, it is thought advisable to bring the collected data from these autopsied cases together for study, and at the same time to report a typical fatal case with autopsy findings.

CASE REPORT

S. W., a white male, aged 53, was admitted to the University Hospital on November 17, 1932, complaining of fever, cough, and shortness of breath. He had lived at Mount Pleasant Beach near Glenburnie, Maryland, and had recently been unemployed. On admission, the patient was very ill and toxic, so that no adequate history could be obtained. Later, it was learned that he had handled a dead rabbit brought in by his dog during the last week in October. On November 2 his present illness began with malaise, fever, and chilly sensations, although there were no definite chills. On November 4 a doctor was called who made a diagnosis of "grippe." The patient improved somewhat and was out of bed for a while on November 7. Later that day he became worse, and the following day his physician told him he had pneumonia. He became steadily worse and entered the hospital on November 17 with a tentative diagnosis of pneumonia.

Physical Examination (November 17) The patient was a well developed, fairly well nourished, middle-aged man, obviously desperately ill. He was propped up in

* Received for publication April 22, 1933.

From the Departments of Medicine and Pathology, University of Maryland, School of Medicine.

bed, very dyspneic, and quite cyanotic. The face was flushed and the patient appeared toxic. He had a tight, non-productive cough. Temperature 104° , pulse 140, respirations 50. There was a moderate conjunctivitis. The teeth were dirty and neglected, the tongue dry, the throat moderately injected. There was no cervical rigidity. *Chest* The heart was negative except for a tachycardia and an occasional extrasystole. Examination of the lungs showed impairment of the percussion note at both bases and many bubbling musical râles, particularly over the areas of impairment. There was no definite change in the breath sounds. *Abdomen* Distended and tympanitic. *Extremities* Old amputation of the right lower leg. Over the dorsal surface of the right hand between the index and third fingers was a freshly healing ulcer about the size of a 25 cent piece. There was a similar lesion on the left hand near the proximal joint of the thumb. The epitrochlear and axillary lymph nodes were not palpable.

Laboratory Findings The urine contained large quantities of albumin, occasional white blood cells and red blood cells, and a few granular casts were noted. The blood picture was normal except for a leukocytic count of 4,000 on November 17 with 78 per cent polymorphonuclear leukocytes in the differential smear. On November 18, the leukocytes had fallen to 3,750. The Kolmer was negative. Because of the history of handling a dead rabbit and the ulcers on the patient's hands, an agglutination for tularemia was requested. This was reported by the University Hospital Laboratory on November 17 as complete at 1:200 and partial at 1:800. A second specimen sent to the Baltimore City Health Department on November 18 agglutinated *B. tularensis* completely at 1:320. A blood culture yielded after 72 hours an organism morphologically *B. tularensis*. This organism produced lesions typical of visceral tularemia in liver, spleen and lymph nodes when inoculated into a guinea pig.

The patient was transferred to the oxygen chamber soon after admission and lapsed into unconsciousness that afternoon. The following day there were palpable glands in the right axilla, increase in abdominal distention with some tenderness, and pulmonary edema. The temperature rose to 106° and the patient died on November 18, one day after admission and 17 days after the onset of his illness. Permission for partial autopsy was granted.

Postmortem Examination On external examination the following pathological changes were observed. Two ulcers were noted on the hands. One was situated on the dorsal surface of the right hand and was irregularly circular. It measured 2 by 1.5 cm. The edges were raised, discolored, and firm, and the base was rather punched out and covered with a dry crust. A similar lesion was present on the left thumb near the metacarpo-phalangeal articulation. There was no edema, little inflammatory reaction and no evidence of lymphangitis in either of these regions. A shotty lymph node was present near the right elbow. A moderately soft gland was present in the right axilla. This node measured about 4 cm. in diameter. The upper chest and neck were markedly suffused and livid. A healed old amputation was noted at the middle third of the right tibia with some muscular atrophy of the thigh on that side.

On opening the thorax a fibrinous exudate was found in both pleural cavities, together with about 100 cc. of cloudy fluid in each side. Patchy organization and friable adhesions were present between the parietal and visceral pleurae. The right lung was extremely heavy and voluminous, and the fibrinous pleural exudate was most marked on the lateral and posterior surfaces. Discrete caseous foci could also be seen in the supralobular tissue. The upper two lobes were almost confluent consolidated and multiple nodular foci could be palpated in the lower lobe. Crepitation was almost entirely absent in this lung. On the sectioned surface a greyish, granular exudate was observed and in the lung tissue discrete areas of caseous necrosis or abscess formation were present (Figure 1). A thick, blood tinged exudate could be expressed from the cut surface of the lobes, and the larger bronchi contained a similar material.

The left lung was very similar to the right, with a fibrinous pleuritis more limited to the apical region, and a pneumonic consolidation involving for the most part the upper lobe. The same discrete foci interspersed with a granular and partly necrotic exudate were observed on the cut surface. The hilar and mediastinal nodes were swollen, and multiple greyish white foci of necrosis were present.



FIG 1 Right lung, showing medial cut surface and lateral pleural surface. Note consolidation of upper lobe with foci of necrosis. The hilar nodes also show necrosis.

The heart weighed 375 grams. The myocardium of the left ventricle measured 18 mm in thickness and grossly was somewhat swollen and pale. The heart was not otherwise unusual. The aorta showed early atherosclerosis. The liver was enlarged, soft and pale, and weighed 2,200 grams. Several pale, white, nodular foci were observed under the capsule. On the cut surface these multiple foci of necrosis were more evident. On the capsule of the spleen and on the peritoneal surface of the diaphragm in this vicinity, there was noted a fibrinous exudate (Figure 2). A few

coils of distended intestine were slightly adherent to the spleen and diaphragm The spleen weighed 350 grams Multiple yellowish foci of necrosis were noted under the capsule The pulp was reddish grey, semifluid, and tended to overflow the capsule The Malpighian bodies were practically obliterated by this swelling of the pulp Yellowish areas of necrosis were present, ranging from milium size to 4 to 6 mm The kidneys, aside from some enlargement and slight subcapsular edema, appeared normal They weighed 250 grams each A moderate amount of hypertrophy of the lateral lobes of the prostate was present without urinary retention



A-1886

Fig. 2. Spleen showing necrosis extending on the capsule and into the pulp.

The bladder appeared normal. The pancreas and adrenals were not unusual. The gastrointestinal tract showed no gross lesions.

The brain was not removed.

Microscopic Examination The primary lesion on the hand was not studied histologically.

Sections from the axillary node showed both discrete foci and confluent areas of necrosis. These necrotic areas were rather acellular, being for the most part composed of granular debris and fragmented nuclear particles. About the margins of these areas were many large, fat-laden phagocytic cells and lymphocytes. Little or no productive reaction was observed. No giant cells were seen. The general architecture of the node was not destroyed, although some edema was noted.

The lesions in the liver appeared miliary in size, a few being slightly larger than a liver lobule. These foci of necrosis in the liver were for the most part situated in portal vein zones. A rather sharp line of demarcation was present between the necrotic material and the liver substance. These foci appeared as areas of acute coagulation necrosis, being composed of granular debris, degenerated liver cells, with pyknotic nuclei and fragmented nuclear particles. Cellular infiltration of a monocytic character with a few polymorphonuclear leukocytes was present about the periphery.

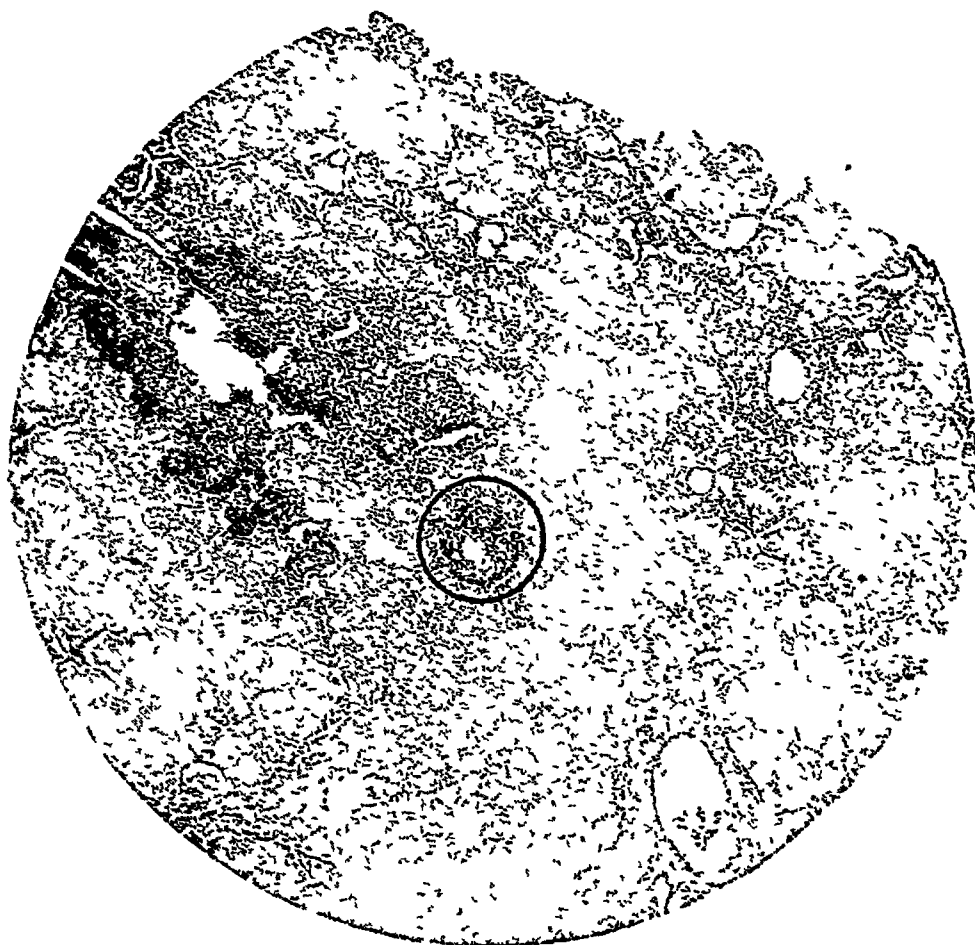


FIG 3 Areas of necrosis in consolidated lung $\times 35$

A few poorly formed giant cells were observed. Some fatty changes were present in the parenchyma but were not related to the foci of necrosis.

Sections from the lung showed an exudative pneumonia that confluentlly involved large areas, in addition to localized foci of necrosis. Many areas showed no air containing alveoli. This exudative process was widespread in sections from the upper lobes. All constituents of the exudate—lymphocytes, polymorphonuclear cells, fibrin, and red blood cells, were in a poor state of preservation, and in localized areas there was necrosis of this exudate as well as lung tissue (Figure 3). These discrete areas appeared identical with the lesions in the liver, node and spleen. A few of these foci were in relation to bronchi and in these areas the bronchial lumen was filled with debris and coagulated exudate. Although the process in many ways presented a similarity to caseous tuberculous pneumonia, no cavitation or acinar-like lesions were seen, and no giant cells observed. One of the most outstanding features was the marked interstitial involvement. There was edema and lymphocytic infiltration of the

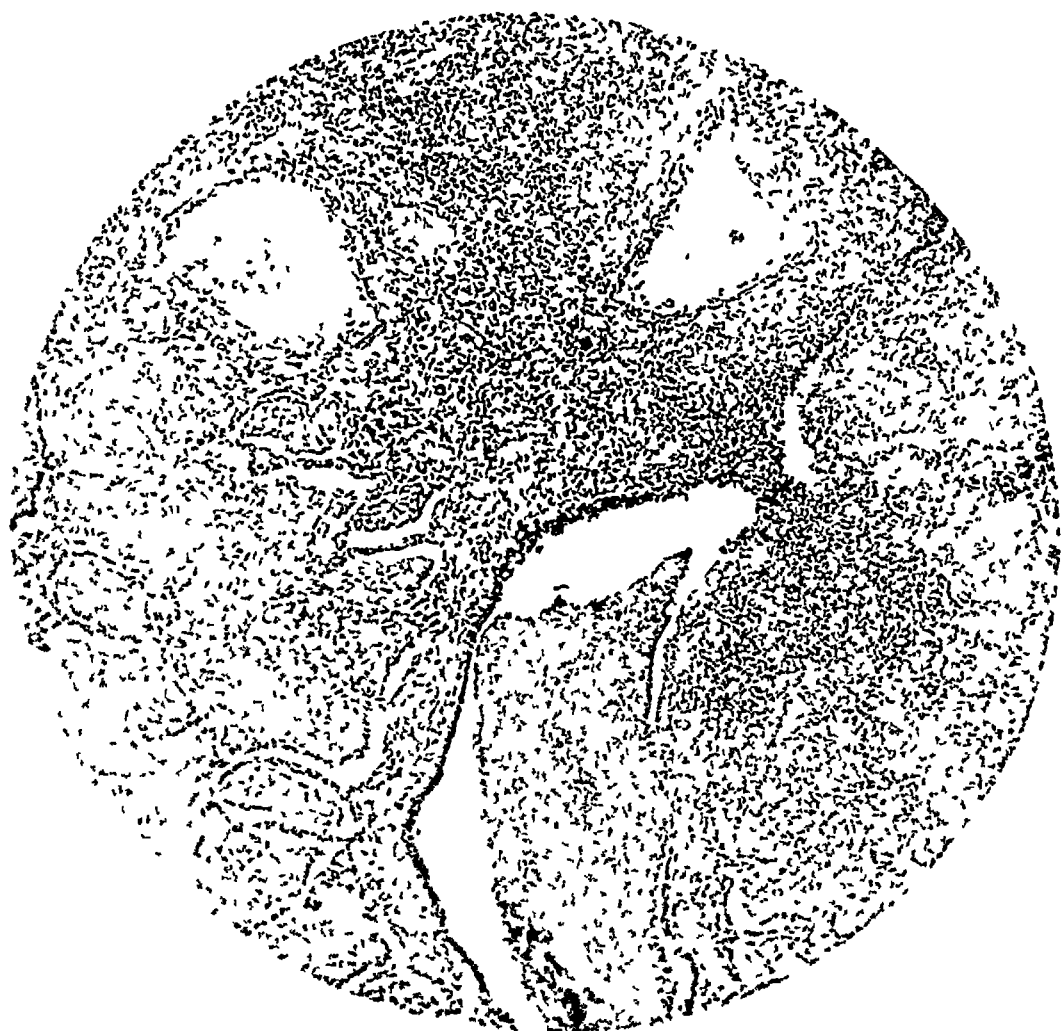


Fig. 4. Interstitial edema and lymphocytic infiltration in the peribronchial tissue with an area of necrosis ulcerating into a bronchus. $\times 120$.

peribronchial and peribronchovascular tissue (Figure 4). The walls of the smaller vessels were thickened and necrotic in this inflammatory process. There was swelling of the walls of the vessels and of many of the small arterioles and venules, in some

instances resulting in thrombosis. This condition may have contributed to the production of the necrosis (Figures 5 and 6)

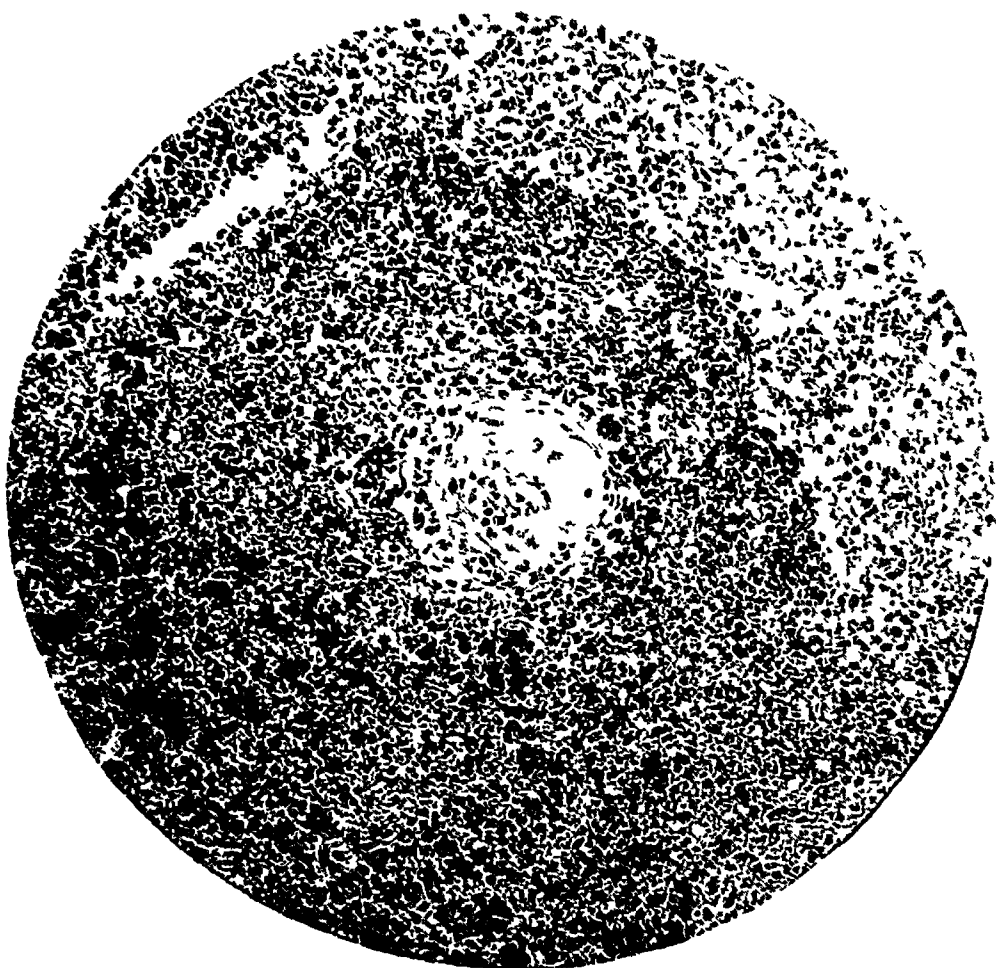


FIG 5 High power of circular area from figure 3, showing thrombus in vessel surrounded by a mantle of necrosis $\times 300$

Sections from the spleen showed a normal appearing pulp and Malpighian body element with typical areas of acute necrosis identical with those described in the liver and node

A section from the diaphragm presented a generalized diffuse reaction consisting chiefly of lymphocytes lying beneath a layer of degenerated and hyalinized fibrin. No local necrotic areas were noted in this exudate

Some tubular degeneration was noted in the sections from kidneys but there were no changes suggesting specific pathology. The histologic changes observed in the heart, pancreas, and adrenals were not unusual. All human tissue in which histological tularemic lesions were observed, were stained by the method employed by Foshay¹⁰ to demonstrate the organism in the lungs. The marked nuclear fragmentation and the accumulation of chromatin particles in and around these lesions made the demonstration of any organism uncertain. Tubercle bacilli were not found.

Bacteriological Examination At autopsy, material from the necrotic foci in the

spleen was macerated and inoculated subcutaneously into a guinea pig. This animal succumbed in five days with the typical visceral lesions of guinea pig tularemia. Another guinea pig was injected with 1 c.c. of a broth culture which had been inoculated with blood taken from the heart of the patient at autopsy. This culture was injected intraperitoneally but this animal developed no tularemic manifestations.

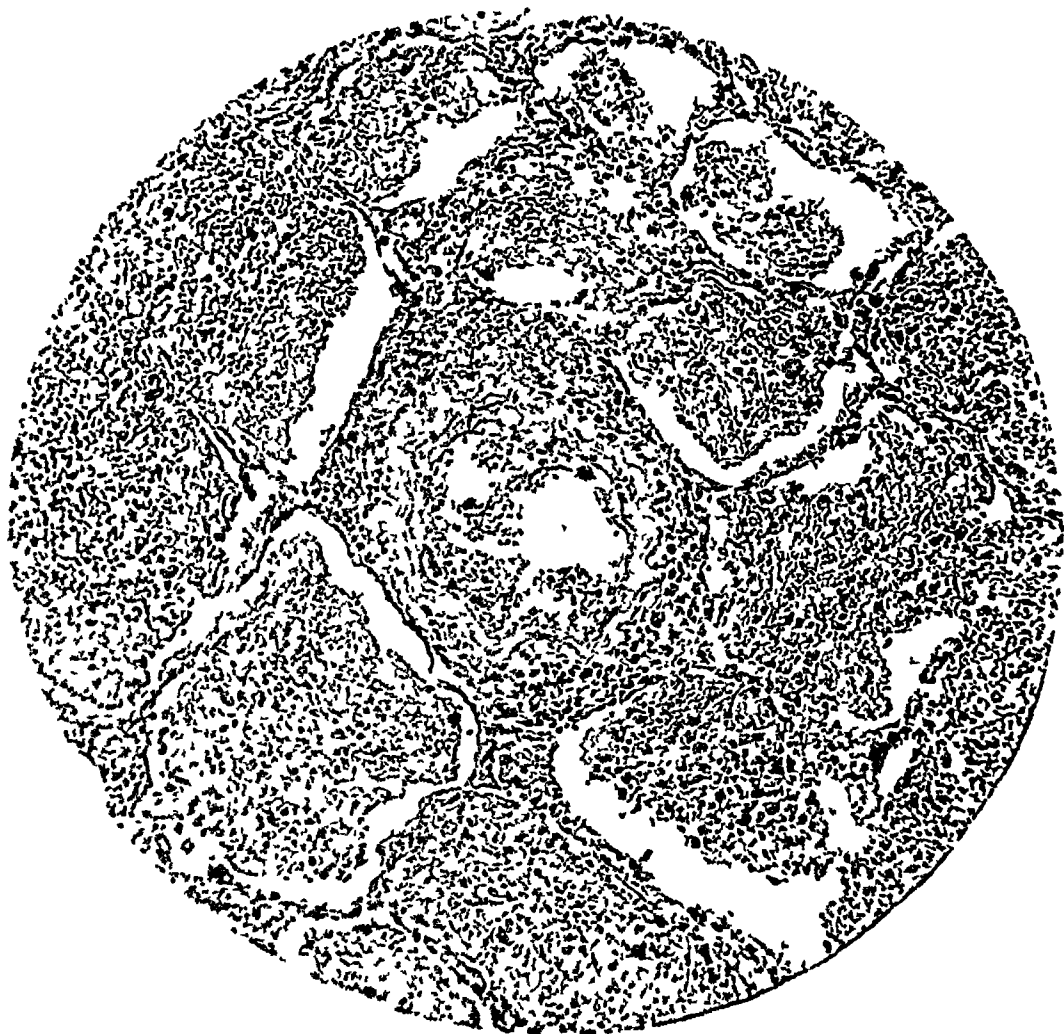


FIG. 6. Vessel in pneumonic area in lung showing subintimal edema. $\times 230$

Blood from the patient taken the day before death was cultured on veal brain broth and dextrose broth. The veal brain broth contained calcium carbonate to produce semi-microbic conditions. A growth was obtained in both, it was more profuse in the veal brain broth. This culture contained an organism morphologically identical with *B. tularensis*. A guinea pig was inoculated intraperitoneally with two cubic centimeters of the veal brain broth culture. This animal died in six days and at autopsy typical tularemic lesions were found.

A search of the literature disclosed reports of 14 fatal cases of tularemia with autopsy. These cases together with our own have been summarized as to clinical and pathological findings in tables 1 and 2. In discussing these tables, the first fact worthy of note is that the 15 autopsied cases re-

ported appear under the names of 15 different authors or groups of authors. That there are so few autopsy reports speaks for the low mortality of tularemia.

The mode of infection was contact with rabbits in 13 cases, contact with an opossum in one, and the bite of a deer-fly in one. The average incubation period in 12 cases (not mentioned in remaining three) was 3.5 days. This exactly corresponds with the incubation period as given by Francis,¹ although one might expect to find a shorter than average incubation period in these fatal cases. The average duration to death was 20 days, Blackford's⁶ case, 41 days, being the longest, and the fulminating case of Simpson,¹³ four days, being the shortest. Fourteen cases were of the ulceroglandular type, and one should probably be classed as typhoidal. Clinically, pneumonia or other lung involvement was a very frequent finding: bronchopneumonia was diagnosed in six cases, lobar pneumonia twice, lung abscess once, and pleural effusion once. The lung involvement often furnished the presenting symptoms and very frequently was the cause of death. In five cases, however, the lung findings were negative.

The average leukocyte count in 12 cases was 10,800, the highest 22,600, in the case of Goodpasture and House⁴, the lowest 3,750, in our own Simpson.¹⁷ gives the leukocyte count in tularemia as ten to fifteen thousand. Poor resistance is suggested by the low average of these counts or rather by the many low leukocyte counts shown in the table. Agglutination tests for tularemia were uniformly negative during the first eight days and uniformly positive thereafter, with steadily increasing agglutination titer as the disease progressed. Thus Blackford's⁶ case (25th day) agglutinated at 1:5120, Hartman's⁹ case (18th day) 1:1280, Bardon and Berdez's¹² (12th day) 1:80. Masee's¹⁶ case demonstrates very well the increasing agglutination titer.

In analyzing the pathological data from the above chart, we find that a lesion at the portal of entry of the organism was found in all but one case, and that the ulceration at this site usually remained until death. The regional glands were involved in all cases, the presence of large caseous peribronchial glands in Permar and MacLachlan's⁵ case, which was without external evidence of a portal of entry, lends credibility to the idea that this case possibly represents an instance of primary respiratory tract infection. In 12 of the 15 cases, either gross or microscopic lesions were noted in the liver. Eleven cases showed necrotic foci in the spleen.

The lungs, next to the regional nodes, were the most constant site of involvement. In Francis and Callender's³ case the postmortem examination was limited to an inspection of the abdominal viscera, but the patient had clinical signs of pneumonic involvement. The remaining 14 cases all showed some pulmonary lesion at autopsy. The most constant lesions in the lungs in these autopsied cases were necrotic foci. This finding was present in 11 cases. Extensive pneumonia was observed eight times, pleural effusion three times, and cavitation and abscess twice.

TABLE I
Clinical Features in Autopsied Cases of Tularemia

Author	Mode of Infection	Incubation	Dura- tion to Death	Type of Infection	Pneumonia or Other Lung Involvement	Leukocyte Count	Agglutination
Verheycke	Housewife dress- ing rabbit	5 days	18 days	Ulceroglandular	No signs men- tioned	12,000 15,400 19,200	1 80 (16th day)
Francis and Callender ¹²	Farmer fly bite	Unknown	26 days	Ulceroglandular	Right upper, rusty sputum	Not reported	Not reported
Schumacher ¹³	Farmer dressing rabbit	Not men- tioned	29 days	Ulceroglandular	No clinical signs	Not reported	Negative (8th day) 1 1280 (19th day)
Birdsall and Berdick ¹⁴	Farmer handling rabbit	1 day	15 days	Ulceroglandular	Bronchopneu- monia, both bases	Not reported	1 160 (10th day)
Goodpasture and House ¹⁵	Dressing rabbits	1 or 3 days	14 days	Ulceroglandular	No clinical mani- festations	15,000 19,000 22,600	Negative (8th day) 1 80 (12th day)
Simpson ¹⁶	Market worker handling rabbits	7 days	4 days	Ulceroglandular	Extensive bron- chopneumonia	15,400	Negative
Palmer and Hansmann ¹⁷	Housewife handling rabbit	3 days	8 days	Ulceroglandular	No clinical signs	9,000	Negative

Bruckner's case (as reported by Francis) is not included in this table The patient died of hemolytic streptococcus septicemia 21 weeks after onset of tularemia.

TABLE I (continued)

Author	Mode of Infection	Incubation	Duration to Death	Type of Infection	Pneumonia or Other Lung Involvement	Leukocyte Count	Agglutination
Bunker and Smith ¹⁵	Hunting and skinning rabbits	5 days	14 days	Ulceroglandular	Signs of effusion	9,400 6,600	Negative at first, low titer last day
Massee ¹⁶	Marketman dressing rabbits	Not mentioned	18 days	Ulceroglandular	Bronchopneumonia both bases	11,500	Negative (8th day) 1 40 (15th day) 1 320 (18th day)
Permar and MacIachlan ⁵	Dressing rabbits	1 day	17 days	Probably typhoidal	Lobar pneumonia, rt upper (late)	7,125 5,200 (17th)	Negative (7th day) 1 320 (17th day)
Bryant and Hirsch ⁸	Chef dressing rabbit	3 days	16 days	Ulceroglandular	No clinical manifestations	7,100	1 40 (14th day)
Hartman ⁹	Butcher skinning rabbit	4 days	36 days	Ulceroglandular	Many râles, left base	11,500 11,400	1 640 (15th day) 1 1280 (18th day)
Foulger, Glazer and Foshay ⁷	Housewife handling rabbit	4 days	21 days	Ulceroglandular	Bronchopneumonia, right	12,000 4,000	1 40 (2nd week)
Blackford ⁶	Negro handling opossum	4 days	41 days	Ulceroglandular	Lung abscess, cough, with foul bloody sputum	8,200	1 40 (9th day) 1 5120 (25th day)
Gundry and Warner	Handling rabbit	3 to 5 days	17 days	Ulceroglandular	Pneumonia, bilateral	4,000 3,750	1 200 (16th day) 1 320 (17th day)

TABLE II
Pathological Findings in Autopsied Cases of Tularemia

Author	Primary Site	Glands	Liver	Spleen	Lungs	Tularemia Lesions Elsewhere	Positive Animal Inoculation
Arbuckle	Right index finger	Regional, enlarged	Studded with necrotic areas	Multiplic necrotic foci	Caseous peribronchial nodes, acute purulent bronchopneumonia, 100 c c in each pleural cavity		Guinea pigs, mice, rabbits, inoc with spleen
Levens and Calkins	Fly bite on rt side neck	Post auricular, right	Incomplete autopsy abdomen exposed Spleen found studded with necrotic foci				From blood fourth day Node and spleen at autopsy
Schumacher	Ulcer, left index finger	Enlarged left axillary	No lesions	Enlarged	No lesions observed	Peritonitis Ulcers-cecum	Not mentioned
Barton and Berdez	Left middle finger	Enlarged axillary	Studded with nodular areas of necrosis	Areas of necrosis	Bronchial glands, caseous nodes in pleura, extensive pneumonia, both bases	Nodules, kidneys	None reported
Goodpasture and House	Rt index finger	Caseous axillary nodes	Enlarged with miliary caseous foci	Enlarged areas of necrosis	Peribronchial nodes, caseous No lesions, lung 200 c c left pleura	Mediastinal and retroperitoneal nodes	From organism recovered ante-mortem blood Axillary node at autopsy

TABLE II (continued)

Author	Primary Site	Glands	Liver	Spleen	Lungs	Tularemic Lesions Elsewhere	Positive Animal Inoculation
Simpson ¹³	Finger	Enlarged and caseous axillary nodes	Multiple necrotic foci	Necrotic foci	Extensive pneumonia with necrosis		
Palmer and Hansmann ¹⁴	Finger	Enlarged and caseous axillary nodes	Areas of necrosis	Yellow necrotic areas	Inconsiderable bronchopneumonia		From heart's blood and axillary tissue
Bunker and Smith ¹⁵	Finger	Caseous regional nodes	No lesions observed	Necrotic foci	28 oz effusion 6 to 8 foci of necrosis		From finger, eighth day, sputum twelfth, autopsy fourteenth
Massee ¹⁶	Thumb	Regional nodes, enlarged	No gross lesion but microscopic necrotic foci	No lesions	Pneumonic consolidation, both bases Confluent lobular pneumonia		From thumb, spleen and lung, all died with typical lesions
Permar and MacIachlan ⁵	Not found, possibly resp tract (?)	Peribronchial nodes enlarged and necrotic	Studded with areas of necrosis	Recent infarct	Lobar consolidation, rt upper Focal areas of necrosis		Not reported
Bryant and Hirsch ⁸	Rt middle finger	Caseous axillary and supra-clavicular	Miliary necrotic foci	Multiple necrotic nodules	Exudative pneumonia with focal necrosis	Leptomeningitis, necrosis subapp tissue	Guinea pig inoculation with spleen, liver and lungs, typical lesions

TABLE II (continued)

Author	Primary Site	Glands	Liver	Spleen	Lungs	Tularemic Lesions Elsewhere	Positive Animal Inoculation
Harmon	Base of left thumb	Left axillary and peribronchial	Necrotic foci present	Microscopic necrosis	Necrotic nodules, left lung	Necrotic areas brain substance, Encephalitis	None reported
Locher, Glick and Loshay	Finger	Axillary nodes	Multiple necrotic areas	Necrotic foci	Caseous abscess, right middle and lower, lobular pneumonia	Peritonitis	Guinea pig inoculated from liver abscesses
Blackford	Left third finger (?)	Enlarged, necrotic left axillary node	No lesions	No lesions	Cavities, rt lower Thrombosis, rt pulmonary art Necrosis in lung		Not reported
Gundry and Warner	Dorsum of rt hand and thumb	Epirochlear and axillary, right	Miliary foci of necrosis	Enlarged necrotic foci	Confluent lobular pneumonia, both uppers Necrosis Fibrinous pleuritis	Localized peritonitis, diaphragm	From blood culture antemortem From spleen at autopsy

The occurrence of lesions other than those of the glands, liver, spleen and lung was infrequent. Baidon and Berdez¹² found lesions in the kidneys, Foulger, Glazer and Foshay,⁷ Schumacher¹¹ and ourselves, lesions on the peritoneum. A new field has been opened up by the more recent reports of Bryant and Hirsch,⁸ and Hartman,⁹ who describe lesions in the brain and meninges.

As regards bacteriology, animal inoculation has proved positive in the majority of these autopsied cases. In two instances the organism was stained in the tissue, Massee,¹⁰ Foulger, et al.⁷ In our own case the organism was cultivated directly from the antemortem human blood.

COMMENT

It is evident from the analysis of the autopsied cases that the pulmonary lesions of tularemia are an important feature of the visceral pathology. This fact has been stressed also by Blackford⁶ and by Permar and MacLachlan.⁵ Francis¹ in his study of 24 fatal cases of tularemia found that more than one-third had shown clinical evidence of pneumonia. Tureen¹⁸ noted that there was a high mortality rate in those cases in which pneumonia developed.

Various types of pulmonary lesions have been described, bronchopneumonia, lobar pneumonia, cavitation, abscess, and pleurisy, with or without effusion, but it would appear that the most characteristic lesion is a lobular type of pneumonia containing foci of necrosis. In the earlier cases that came to autopsy the localized necrotic lesions only were considered to be due to tularemia. The more diffuse patches of consolidation were interpreted as a secondary bronchopneumonic process. More recently the closer histological study of these pneumonic areas and the demonstration by Massee¹⁰ and by Foulger, Glazer and Foshay⁷ of the *B. tularensis* in the pulmonary exudate has led to the acceptance of the view that all of the pulmonary pathological lesions are due to the tularemic infection. Our own histological observations are in accord with those of Permar and MacLachlan.⁵ We feel that the outstanding features of the pulmonary lesions may be summarized as follows: the process is a confluent lobular pneumonia with marked involvement of the interstitial tissues, the exudate contains a predominant number of lymphocytic cells, vascular lesions are found characterized by subintimal edema, often associated with thrombosis. These vascular occlusions offer the best explanation of the areas of necrosis which are typical features of tularemic pathology.

Attention should be drawn again to the resemblance of pulmonary tularemia to pulmonary tuberculosis. It is probable that at times the gross pathological pictures have been confused. It should be noted also that the clinical picture of tularemic pneumonia might readily be mistaken for an ordinary bronchopneumonia or an atypical pneumococcal lobar pneumonia.

The second most frequent site of involvement in the fatal cases reviewed was the central nervous system. Francis and Callender³ in 1927,

in discussing a fatal case without autopsy, first suggested on the basis of the clinical findings that meningeal or cerebral lesions were probably present. In 24 fatal cases reported by Francis¹ in 1928, it was noted that five had died in coma. Later Bryant and Hirsch⁸ in a case with clinical symptoms of meningitis reported a marked pleocytosis in the spinal fluid and at autopsy the presence of a leptomeningitis. Hartman's⁹ case was admitted with fever and delirium, at autopsy a diffuse encephalitis was found.

REFERENCES

- 1 FRANCIS, E. Symptoms, diagnosis and pathology of tularemia, Jr Am Med Assoc, 1928, xci, 1155-1161
- 2 VERBRICKE, J R, JR. Tularemia, with report of fatal case simulating cholangitis, with postmortem report, Jr Am Med Assoc, 1924, lxxxi, 1577-1581
- 3 FRANCIS, E, and CALLENDER, G R. Tularemia, microscopic changes of lesions in man, Arch Path and Lab Med, 1927, iii, 577-607
- 4 GOODPASTURE, E W, and HOUSE, S J. Pathologic anatomy of tularemia in man, Am Jr Path, 1928, iv, 213-226
- 5 PERMAR, H H and MACLACHLAN, W W G. Tularemic pneumonia, ANN INT MED, 1931, v, 687-698
- 6 BLACKFORD, S D. Pulmonary lesions in human tularemia, pathological review and report of fatal case, ANN INT MED, 1932, v, 1421-1426
- 7 FOULGER, M, GLAZER, A M, and FOSHAY, L. Tularemia, report of case with post-mortem observations and note on staining of *Bacterium tularensis* in tissue section, Jr Am Med Assoc, 1932, xcvi, 951-954
- 8 BRYANT, A R and HIRSCH, E F. Tularemic leptomeningitis, report of case, Arch Path, 1931, xii, 917-923
- 9 HARTMAN, F W. Tularemic encephalitis, pathology of acute tularemia with brain involvement and coexisting tuberculosis, Am Jr Path, 1932, viii, 57-62
- 10 FOSHAY, L. Personal communication
- 11 SCHUMACHER, H W. Cited by FRANCIS, E. (Personal communication to author), Jr Am Med Assoc, 1928, xci, 1155-1161
- 12 BAXTON, R, and BERDEZ, G. Tularemia, report of fatal case, with postmortem observations, Jr Am Med Assoc, 1928, xc, 1369-1371
- 13 SIMMONS, W M. Tularemia (Francis' disease) clinical and pathological study of 48 non-fatal cases and one rapidly fatal case with autopsy, occurring in Dayton, Ohio, ANN INT MED, 1928, i, 1007-1059
- 14 PALMER, H D, and HANSMANN, G H. Tularemia, report of fulminating case with autopsy, Jr Am Med Assoc, 1928, xci, 236-239
- 15 LUTZ, C W O, and SMITH, E E. Tularemia, report of four cases, one fatal with autopsy report, U S Naval Med Bull, 1928, xxxi, 901-911
- 16 MCGEE, J C. Tularemia in Georgia: report of a fatal case, Jr Med Assoc Ga, 1931, xvi, 67
- 17 SIMMONS, W M. Tularemia: history, pathology, diagnosis and treatment, 1929, Paul B. Hoeber, New York
- 18 FOSHAY, L. Tularemic pneumonia, Jr Am Med Assoc, 1932, xcix, 1501-1502

FRAGILITAS OSSIUM IN FIVE GENERATIONS *

By HENRY JOACHIM, M D , F A C P , and MILTON G WASCH, M D ,
Brooklyn, New York

WE HAVE HAD the opportunity of seeing eight cases of fragilitas ossium in one family covering three generations, and have been able to trace the disease in five generations. We present a report of three of these cases.

CASE I

Dora B, 43, married, was admitted to the Israel Zion Hospital in January 1932 with the complaint of headaches and dizziness of several months' duration.

Previous History The patient began to walk at the age of five years. In childhood she had abscessed ears which caused some impairment of hearing. Her menstruation had always been irregular. The last period was in October 1931. She had had five children. There had been no miscarriages. As long as she could remember, she had been subject to "sprains" of her hands and feet from the slightest cause, such as lifting a pail. On one occasion she sustained a fracture of her thigh from tripping.

Physical Examination Short, obese female, weighing 194 pounds. The sclerae were of a striking blue color, a cerulean blue. On inquiry as to the presence of blue sclerotics in any other members of her family, she volunteered the information that her family was known as "the people with the blue eyes." Inspection also revealed deformities of the hands produced by flail-like joints. Many members of her family were double jointed. Her feet were markedly flattened from ligamentous relaxation.

Her blood pressure was 170/110. The eyegrounds showed slight vascular sclerosis. Otherwise physical examination was negative.

Urine sp gr 1020, faint trace of albumin, many calcium oxalate crystals, occasional pus cells, no casts. Red blood cells 4,000,000, white blood cells 10,600, hemoglobin 95 per cent. The differential count showed 43 per cent of polynuclears, 47 per cent lymphocytes, 9 per cent mononuclears, and 1 per cent basophiles.

Blood Chemical analyses

Urea N	16 mg
Uric A	4.2 mg
Chlorides	475 mg
Cholesterol	275 mg
Glucose	75 mg
Creatinine	1.5 mg
Phosphorus	3 mg
Calcium	8.0 mg

The blood calcium determination was repeated and gave a reading of 9.8 mg.

Extensive roentgen-ray studies of the osseous system were made. Two of these roentgenograms are shown in figures 1 and 2.

A diagnosis of fragilitas ossium and essential hypertension was made.

CASE II

A. B, age 9 1/2, daughter of patient in case I.

Previous History In infancy the patient was breast fed for five weeks, but the

* Accepted for publication October 26, 1933.

From the Departments of Medicine and Radiology of the Israel Zion Hospital, Brooklyn, N. Y.

mother then sustained a shock and was unable to continue nursing so that artificial feeding was instituted. The child suffered from frequent attacks of vomiting and diarrhea. At the age of five weeks, the mother lifted the child out of the bath tub and fractured an arm. At the age of eight months, a leg was fractured. At 19

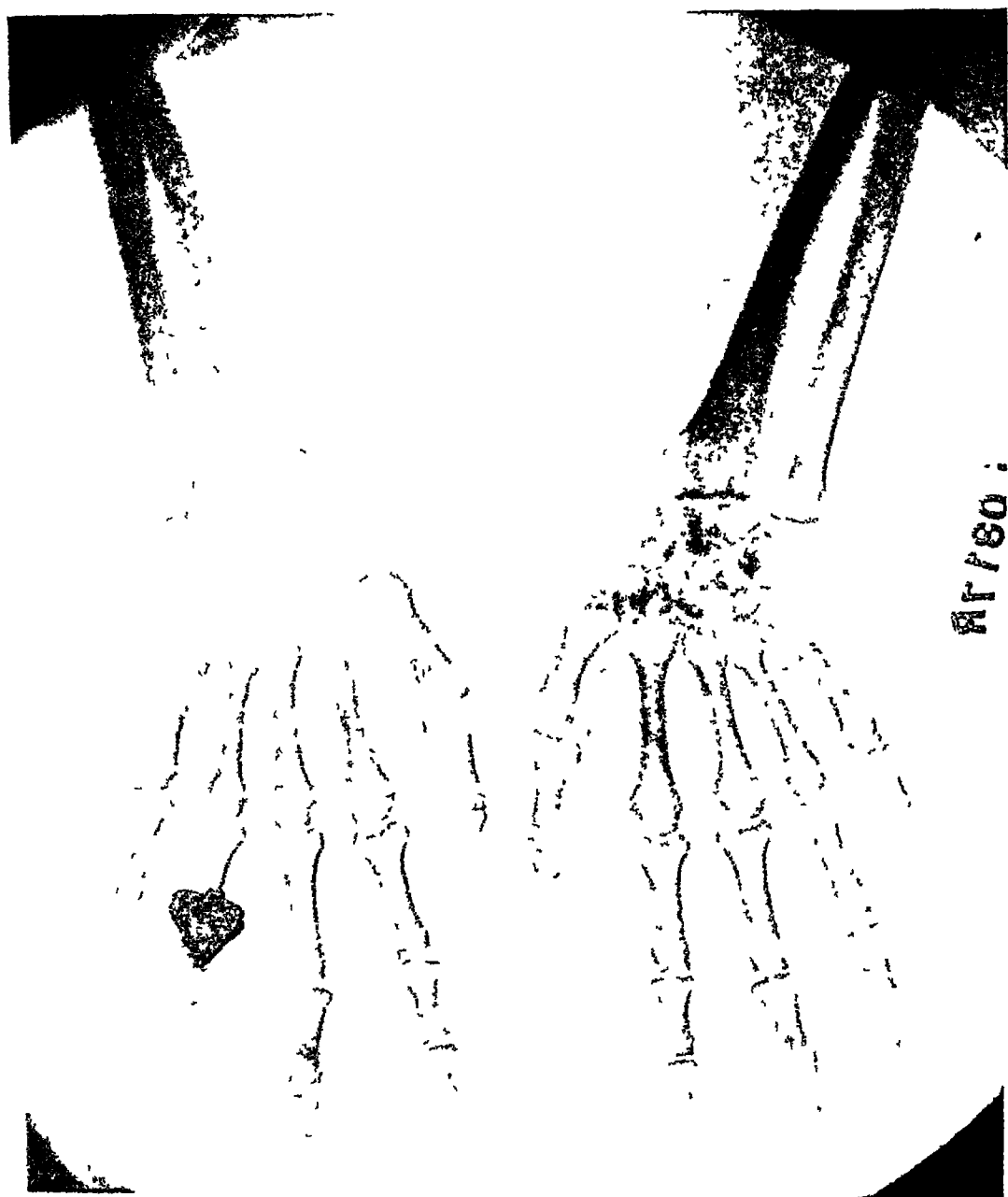


Fig. 1. Rickets of both forearms. Extremities of metacarpals broadened, with shaft narrowing producing dumb-bell effect.

The child began to walk. At 23 months, she fell from a chair and fractured her right arm. At 29 months she fractured the left humerus, and this was followed by a fracture of the other humerus. In all there have been 18 recorded fractures. One year ago her school physician noticed a painless spinal curvature. She has also had a fractured vertebra, for which she is still wearing a brace. Since birth the child's extremities have always been cold. She has

Physical Examination Weight 79 pounds The sclerae are of a deep blue color There is a marked spinal scoliosis, and a well developed pes planus There are many ecchymotic spots over the body

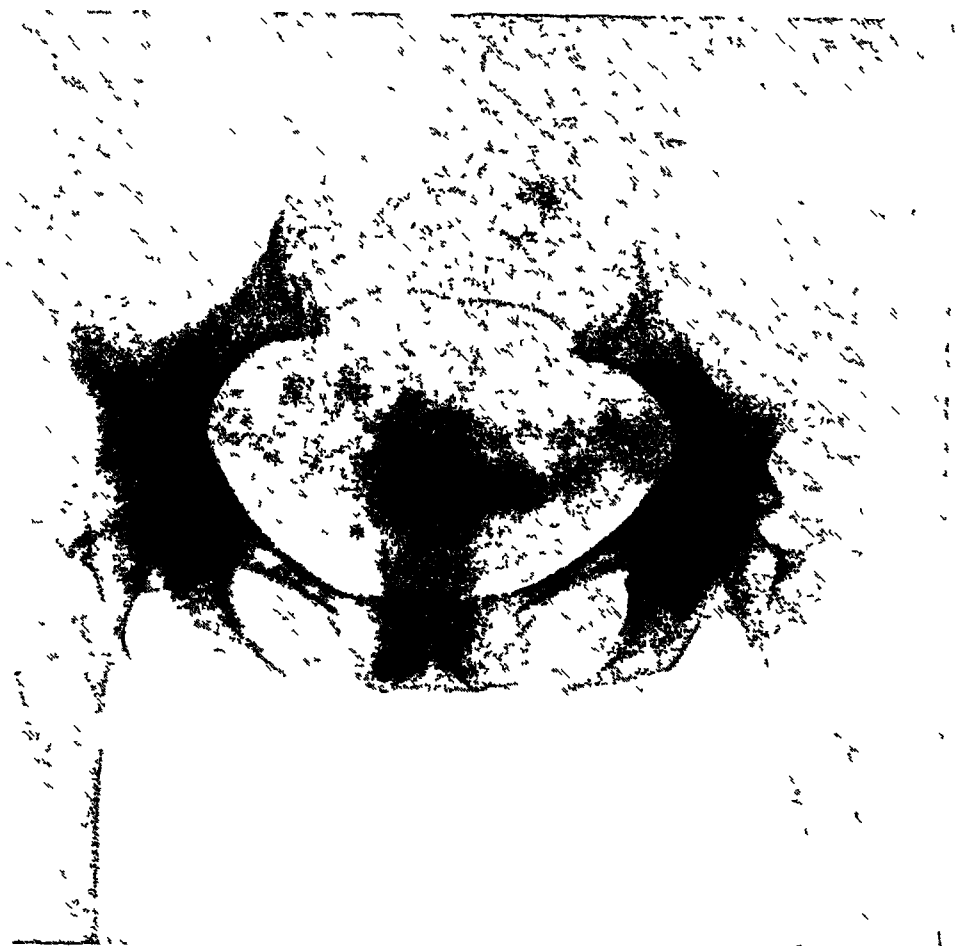


FIG 2 Flat pelvis Note compensation of the transverse diameter for the foreshortened antero-posterior Defect lower left aspect of the body of the third lumbar vertebra, incident to mild trauma

Blood Chemical analyses (January 1932)

Calcium	50
Phosphorus	35
Cholesterol	2650
Chlorides	4750

The calcium and phosphorus determinations were repeated about four weeks later and were reported as calcium 90 and phosphorus 55 The basal metabolic rate was plus two Numerous roentgenograms of the osseous system were made, two of which are shown in figures 3 and 4

CASE III

S. R., age 13, a niece of the patient in case 1

Previous History The child had been breast fed until 15 months of age. She was then placed on whole milk to the amount of five to six quarts daily, to the ex-



Fig. 3. Characteristic osteoporosis of lower tibia and fibula, tarsal and metatarsal bones. Note thinness of cortex of all bones, with well demarcated trabeculation throughout. Plantar flexion altered, caused by ligamentous relaxation.

clusion of other foods. At the age of 18 months, she fractured her right hip, at 22 months the right leg, and two weeks later the right wrist. At the age of four years the right leg was fractured and two months later the right ankle. Since then she has had many other fractures from the slightest trauma. Since the age of eight years she has had a discharging left ear. The menses began about five months ago.

Physical Examination A pituitary type of individual, weighing 131 pounds, with blue sclerae, relaxed joints, marked pes planus and genu valgus. The teeth were deformed and defective.

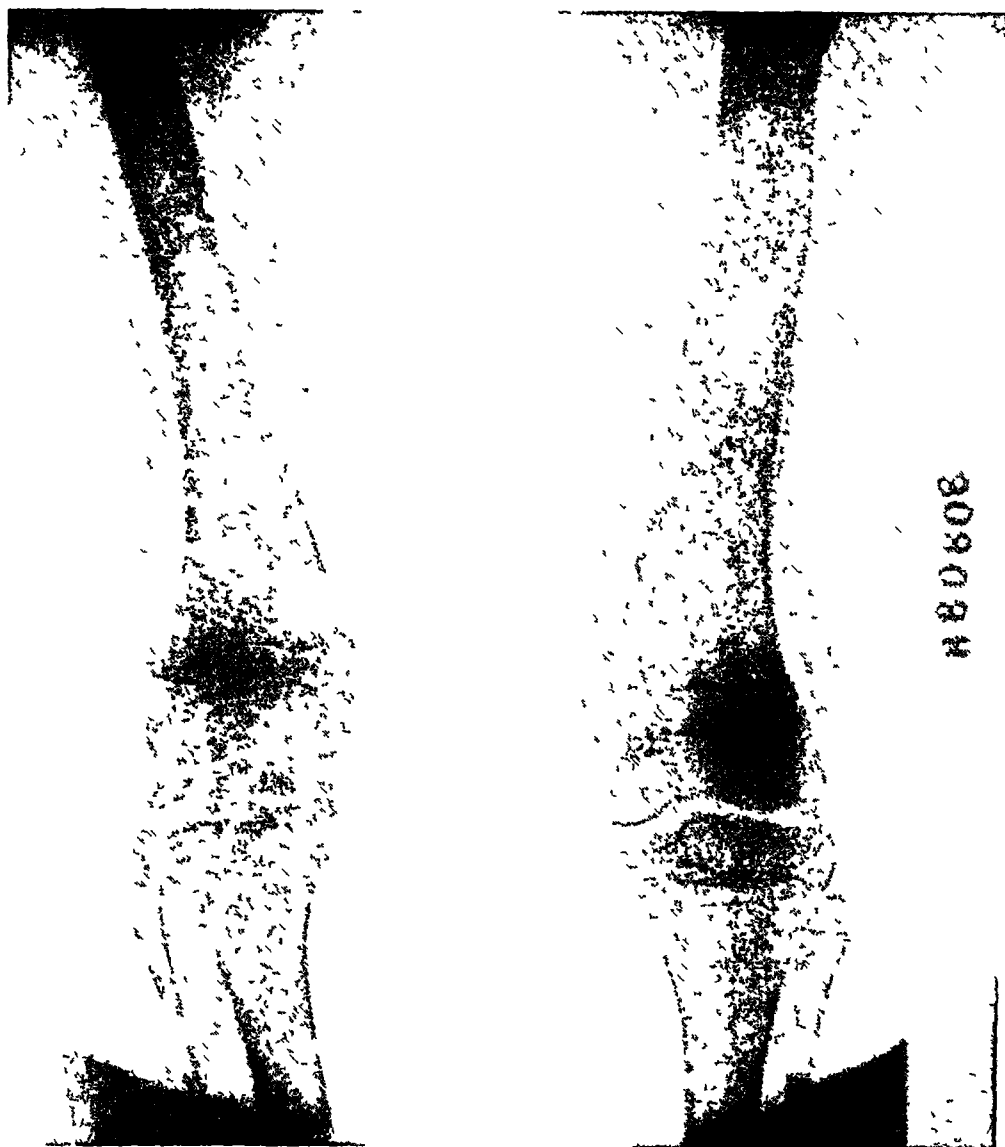


FIG 4 Subperiosteal proliferation (clinically painless) lower right femur, of recent mild traumatic origin. Note curvature of bone above and slight sclerosis, the end result of previous fractures. Metaphyses and epiphyses of both knees markedly reticulated and decalcified. Dense transverse metaphyseal lines, indicating progressive zones of calcification.

Blood Chemical analyses

	January 1932	March 1932
Chloride	480	450
Cholesterol	290	
Phosphorus	3.5	5.5
Calcium ..	7.0	9.7

The basal metabolic rate was plus two. Roentgenographic studies were made, two of these roentgenograms are shown in figures 5 and 6

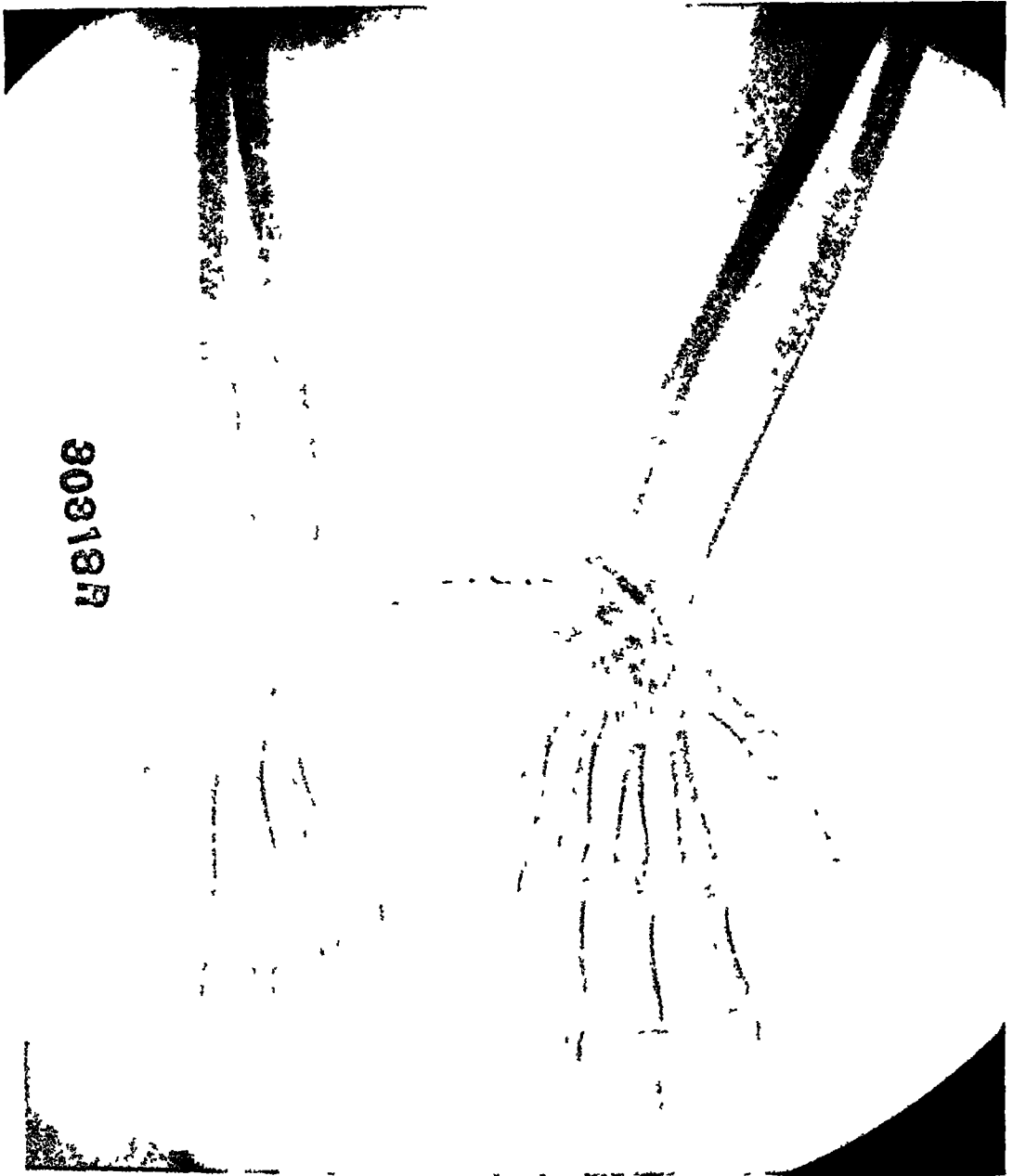


FIG. 5. Prominent phleboscrosis. Subcutaneous venous network visible throughout the length of both forearms.

We append an illustration of the family tree of these patients (figure 7). We have personally seen members of three generations of this family, and we have obtained a history of the existence of this disease in two other generations from three independent sources.

DISCUSSION

The three cases studied were 43, 13 and 9 1/2 years of age. Aside from the characteristic findings in the roentgen-ray studies, a distinct prominence

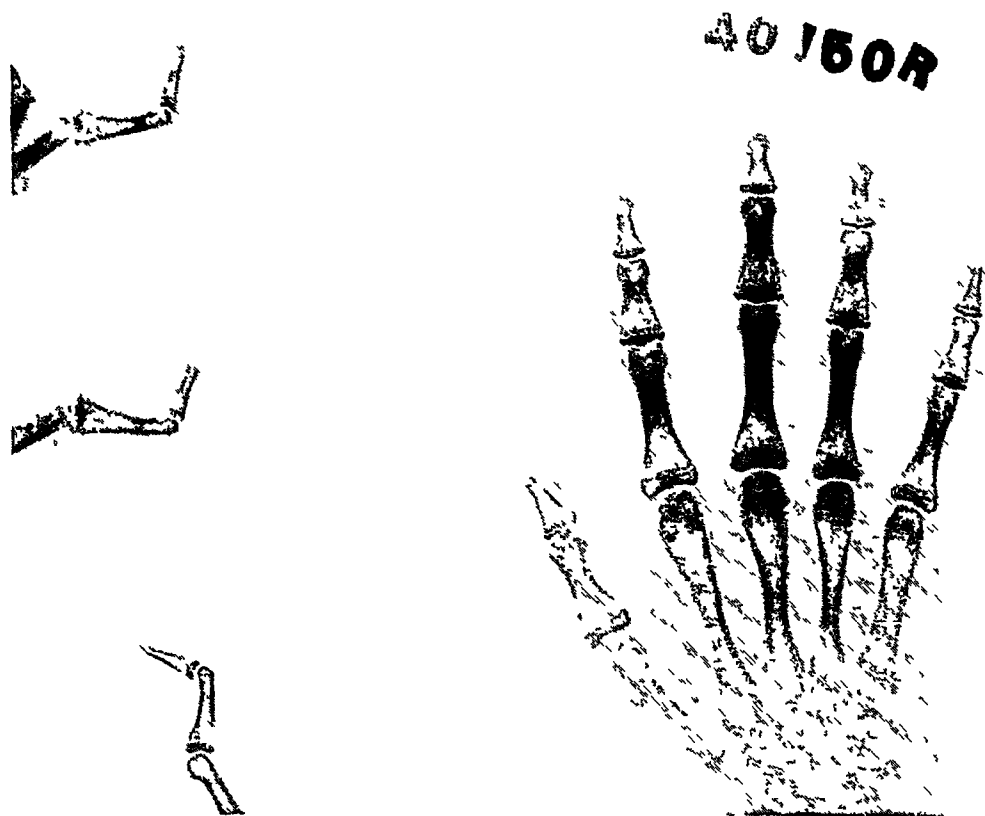


FIG 6 Osteoporosis, with articular relaxation, giving rise to double-jointed index finger
Dumb-bell metacarpals

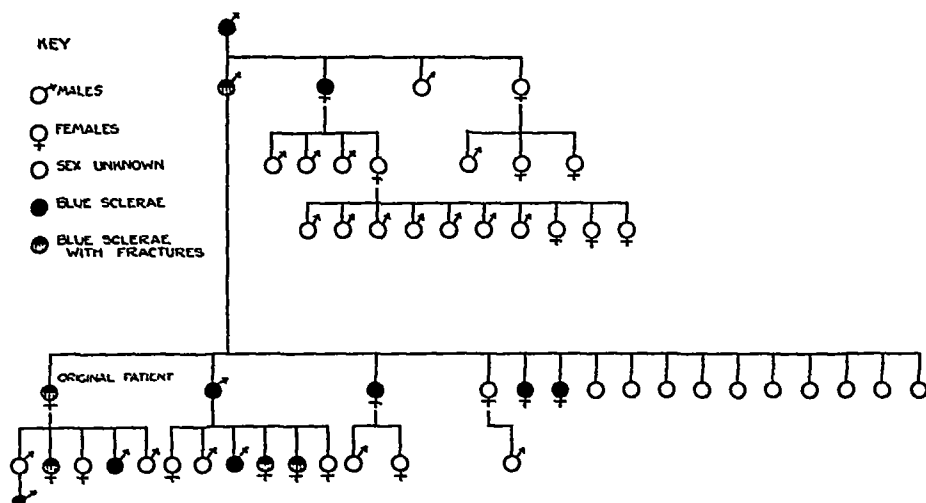


FIG 7 Family tree of five generations of fragilitas ossium

of the veins, indicating sclerosis, was noted in each of the three cases. The thinning of the shafts of the metatarsal and metacarpal bones producing relative enlargement of the head and the base, and giving the "dumb-bell" type bones, also warrants special mention. Studies of calcium in the blood were not conclusive. In one case oxaluria was reported.

CONCLUSIONS

Fragilitas ossium was traced through five generations of one family. It was associated with blue sclerae. Some of the cases sustained multiple fractures, others presented a distinct ligamentous relaxation, causing the condition known as double-jointedness. Phlebosclerosis was noted in all three of the cases studied.

We wish to thank Dr. Alfred F. Hess of New York for seeing these three cases with us, and Dr. M. Goldzieher and I. Sherman for the laboratory examinations.

A JUSTIFICATION OF THE DIAGNOSIS OF CHRONIC NERVOUS EXHAUSTION *

By JOHN W MACY, M D , and EDGAR V ALLEN, M D , F A C P ,
Rochester, Minnesota

"CHRONIC NERVOUS EXHAUSTION," a term synonymous in the minds of many persons with neurasthenia, psychasthenia, or neurocirculatory asthenia, lacks the clear-cut connotation of terms such as duodenal ulcer or pulmonary tuberculosis. The symptoms of chronic nervous exhaustion are protean, they may appear to originate in any or all bodily structures and systems. In its most common meaning, chronic nervous exhaustion indicates a long-present, subjective sensation of tiredness, disproportionately exceeding the effort which produces it and which cannot be accounted for by organic disease. Weakness, lack of energy and ambition, nervousness, unrestful sleep or insomnia, melancholia, tachycardia, and pains and aches in various parts of the body may be additional symptoms of the condition. The syndrome mentioned may be associated with organic disease, yet not occur as a direct result of it, but rather indirectly, as a result of the worries and uncertainties precipitated by organic disease that is recognized to be present by the patient.

The term chronic nervous exhaustion has little standing with many physicians, to them it is an admission of inability to indicate the situation or nature of an organic change that is responsible for the symptoms. To others the diagnosis is as significant and inclusive as that of chronic mitral endocarditis, for example. It is not germane to our subject to consider the respective viewpoints, although we accept chronic nervous exhaustion as an accurate diagnostic term. Nor is it the purpose of this presentation to consider the genesis of chronic nervous exhaustion, the means of distinguishing it from such conditions as psychoneurosis and constitutional biologic inferiority, or the manner of treatment of and the outlook for patients with this condition. It is well to keep in mind that the accuracy of the diagnosis of chronic nervous exhaustion should bear a direct relationship to the accuracy of the diagnosis of other conditions, depending on the caliber and equipment of the responsible physician or physicians.

For our investigation, we selected case records of patients examined at The Mayo Clinic, each acceptable case record was that of a patient who had been seen at the Clinic one or more times several years after the original diagnosis of chronic nervous exhaustion had been made. In these records we hoped to be able to trace the evidence of organic disease, if such were present, and to determine the tenability of the diagnosis of chronic nervous exhaustion. We assumed that if the clinical picture at the first examination

* Submitted for publication March 25, 1933

From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota

was due to unrecognized organic disease, such organic disease should be detected by a subsequent examination or examinations over a period of years. The objections to such an assumption seem minor, the almost uniform tendency of organic disease is to progress, and to become, therefore, more obvious, or to improve and to lead to disappearance or diminution of the symptoms produced. Moreover, repeated examinations minimize the possibility of diagnostic error.

MATERIAL STUDIED

Our material consisted of the records of 235 patients who were reexamined at The Mayo Clinic an average of six years after the original diagnosis of chronic nervous exhaustion had been made. In each case our study began with the original diagnosis of chronic nervous exhaustion. The entire number of patients may be divided into three groups, consisting of (1) patients who did not ever have organic disease, (2) patients who, at the time of the final examination, had organic disease that was not considered responsible for the original symptoms, and (3) patients who were found, subsequent to the time of the original diagnosis of chronic nervous exhaustion, to have organic disease which appeared to explain, at least in part, the symptoms originally complained of.

Group 1 (Patients who did not have organic disease) This group is composed of 200 patients, 85 per cent of all patients studied. An average of about six and a half years elapsed between the original and the final examinations. The minimal period between the time of the first and last examinations was two years. No organic disease had developed subsequent to the original examination. It cannot be reliably concluded from this series of cases that patients with chronic nervous exhaustion fail to recover from the symptoms of which they complain. Doubtless many patients improve or are entirely relieved, and because of this do not return for reexamination. Those who fail to receive the benefit mentioned are likely to return for further opinion regarding their condition.

Women comprised 78 per cent of the group, 25 per cent of whom were single and 6 per cent widowed or divorced. Forty per cent of the entire group of men and women were in the fourth decade of life, and about 20 per cent in each of the third, fifth and sixth decades of life. Thirty-four per cent of the women were housewives, and 15 per cent were teachers, a variety of occupations was recorded for the remainder of the women patients. Eight of the 44 men were farmers, five were physicians, four were lawyers and one was a dentist, the remainder of the group were of various occupations, such as merchants, bankers and laborers.

The duration of the symptoms in this group of cases ranged from three weeks to 46 years, and averaged about five years, in only 18 instances were the symptoms of shorter duration than one year.

It is difficult to give accurately the part of the body concerning which the patients complained when relating their symptoms; in most instances the

symptoms were multiple, and appeared to originate from more than one organ or system. The points of origin of the major symptoms were as follows: gastrointestinal tract, 69 cases, nervous system, 60 cases, muscular system, 37 cases, thyroid gland, 20 cases, and heart, 14 cases. The symptoms referable to the gastrointestinal tract were chiefly bloating and belching, soreness of the abdomen, constipation, eructation, and indefinite types of distress, those referred to the nervous system were nervousness, insomnia, headache, unrestful sleep, fatigue, emotional instability, and mental depression. The symptoms which apparently arose in the muscular system were weakness, fatigue, and indefinite aches and pains. Twenty patients complained of "goiter," and their chief symptoms were those listed as arising in the nervous system, or apparent enlargement of the thyroid gland. The chief symptoms referable to the heart were palpitation, tachycardia, and irregular rhythm. The following two cases are illustrative of the wide divergence in the type and duration of symptoms.

A woman, aged 50 years, had been in poor health most of her life, bloating, belching and abdominal discomfort had been present for 15 years. The same symptoms were present at the second examination 10 years after the original diagnosis of chronic nervous exhaustion had been made. Three major surgical procedures on the abdominal and pelvic organs had been carried out since the onset of the symptoms referred to the gastrointestinal tract, relief was not experienced.

A merchant, aged 56 years, had noticed dizziness and lack of energy following the death of his business partner three weeks previously, at that time his responsibilities and business cares had increased greatly. He was reexamined 10 years later, at which time he stated that the symptoms noted at the time of his first examination had disappeared shortly after readjustment of his business.

This group of 200 patients had undergone a total of 289 separate operations, of these tonsillectomy accounted for 74. The remaining operations appeared to have been performed in most instances for relief of the same symptoms that were mentioned at the time the diagnosis of chronic nervous exhaustion was made at The Mayo Clinic. Eighty-one of the 156 women in this group of patients had undergone operations on the pelvic organs: uterine suspension, hysterectomy, plastic repair of cystocele and rectocele, or removal of oviducts, of ovaries or of ovarian cysts. Removal of the appendix, gall-bladder, thyroid gland, hemorrhoids, and surgical procedures on the accessory nasal sinuses accounted for the remainder of the operations. Failure to obtain relief in the majority of cases is indicated by the fact that the examinations at the Clinic were made on account of the symptoms for which the operations had been performed.

The points of significance in the records of the patients who comprise this group are the predominant proportion of women, the fact that a large proportion of the men were of "white collar" occupations, that the type and duration of symptoms were of wide range, and that numerous operations were performed for symptoms which were not relieved in the majority of instances.

Group 2 (Patients who, at the time of the final examination, had organic disease that was not considered responsible for the original symptoms) There were 21 patients in this group which comprises 9 per cent of all cases studied. The patients were reexamined at an average of seven years after the original examination. In all of the cases organic disease had developed (table 1). Patients were included in the group only if review of their

TABLE I
Summary of Final Diagnoses in Group 2

Diagnosis	Time, years*
Cholelithiasis (2 cases)	10 and 5
Duodenal ulcer (2 cases)	7 and 6
Carcinoma of breast (2 cases)	1 and 2
Carcinoma of uterine cervix (2 cases)	7 and 8
Menorrhagia	11
Gastric hemorrhage (?)	8
Leukemia†	7
Exophthalmic goiter (10 per cent possibility)	10
(cholecystitis ?)	9
Nontoxic adenomatous goiter (2 cases)	3 and 9
Pulmonary tuberculosis	10
Hypertension and arthritis	4
Bronchogenic carcinoma	10
Septicemia	6
Syphilis of central nervous system	5

* Between original and final diagnosis

† Number of leukocytes in each cubic millimeter of blood was normal at the first examination

records indicated that the eventual organic disease could not, in all probability, have been responsible in any degree for the symptoms originally noted. Although such a relationship cannot be proved or disproved with certainty, whenever doubt existed in our minds whether a certain patient should be considered in group 2 or group 3, the latter classification was used. In several instances in group 2, relationship of the organic disease to the original symptoms was disproved by the factor of time alone, carcinoma of the uterine cervix, leukemia, bronchogenic carcinoma, and septicemia could not have been present for seven, seven, ten, and six years, respectively, before their recognition. They could not, therefore, have been responsible for the original symptoms.

Group 3 (Patients who were found, subsequent to the time of the original diagnosis of chronic nervous exhaustion, to have organic disease which appeared to explain, at least in part, the symptoms originally considered it). There were 14 patients in this group, comprising about 6 per cent of the entire number studied. The patients were reexamined at an average of five years after the diagnosis of chronic nervous exhaustion had been made. All of them, except the patient with paroxysmal tachycardia, had organic disease at the time of the final examination. Although it is difficult to determine in any specific instance whether the organic disease

existed at the time of the diagnosis of chronic nervous exhaustion, consideration of the entire group leads us to believe that in some instances such was the case. It is impossible in most instances to determine whether the diagnosis of chronic nervous exhaustion was erroneous in the sense that closer examination would have revealed organic disease, or whether the organic disease was in such an early stage that it could not have been recognized clinically. We believe that in most instances in which the latter was true, the final diagnosis of organic disease accounted for the earlier symptoms.

Three conditions account for the organic diseases found in eight of the 14 cases in this group, namely, chronic encephalitis in three cases, hyperthyroidism in two cases and tuberculosis in three cases. The early symptoms of these three diseases tend to be vague or of little localizing value. Moreover, chronic fatigue is often one of the earlier symptoms of these conditions.

In two of the cases of chronic encephalitis the presence of organic disease was suspected at the time the diagnosis of chronic nervous exhaustion was made, but evidence of it was inconclusive. In the remaining case of this type, the disease was not suspected.

In both of the cases in which hyperthyroidism was finally recognized, it was suspected initially, because of the basal metabolic rate, but was not confirmed at that time.

One of the three patients who were finally found to have tuberculosis gave a history highly suggestive of tuberculous infection of the lungs, but the physical and roentgenographic examinations of the lungs did not confirm the suspicion. It is possible that pulmonary tuberculosis was present but unrecognized. In another of the cases of this type, either the diagnosis of healed tuberculosis at the primary examination was fallacious, or else reactivation of the infection had occurred. In the remaining case, pulmonary tuberculosis which apparently was suspected at the time of the original examination could not be demonstrated.

Six cases of the 14 remain to be accounted for. In the first of these, organic disease was suspected but not diagnosed at the time of the first examination, appendiceal abscess was finally discovered. Concerning the second case, it is impossible to state that syphilis of the central nervous system, which was recognized at the second examination, was responsible for the symptoms at the first examination. Careful survey of the records of the final examination of the third patient did not indicate sufficient reason to suspect the presence of typhoid fever although seven weeks after the patient left the Clinic, we were informed, by letter, that she had died of this disease. The original diagnosis of chronic nervous exhaustion made 10 years previously appears to have been reliable. In the fourth instance, the diagnosis of chronic nervous exhaustion apparently was a frank error. Enlargement of the cervical lymph nodes was present, and two weeks later

this was found to be part of the syndrome of Hodgkin's disease. The original diagnosis in the fifth case may represent oversight, inasmuch as the urine contained leukocytes and erythrocytes, five years later, nephrolithiasis was discovered. The original diagnosis of chronic nervous exhaustion in the sixth case could well have been entirely reliable, but more than two years later definite paroxysmal tachycardia was recognized.

A summary of the 14 cases of group 3 shows that in only four instances did the original examiners fail to suspect the presence of an organic disease that almost certainly was responsible for the original symptoms. The paroxysmal tachycardia that appeared in another case was not caused by organic disease, but the original diagnosis of chronic nervous exhaustion may be considered in error inasmuch as it did not adequately explain the episodes of palpitation. These five cases represent errors in the diagnosis of chronic nervous exhaustion, if the term error be reserved for instances in which the examining physician was frankly at fault. They comprise only 2.1 per cent of the total number of 235 cases in which the original diagnosis of chronic nervous exhaustion was made.

COMMENT

If one considers that all cases of groups 2 and 3 represent errors in the diagnosis of chronic nervous exhaustion, the proportion of error is 15 per cent. If only the five cases of group 3 that have been mentioned are accepted as evidence of faulty diagnosis, and this seems more just, the proportion of error is 2.1 per cent. In other words, the greatest possible error in the diagnosis of chronic nervous exhaustion made under such circumstances as those presented is 15 per cent and the least error is 2.1 per cent. The percentage in our series of cases probably lies between the two mentioned, it appears to be about the 6 per cent represented by the 14 cases of group 3.

This impresses us as a gratifyingly small error when it is considered that the diagnosis of chronic nervous exhaustion cannot be made on the basis of objective findings but is, rather, based on the paucity of objective findings in addition to the results of careful study of the symptoms presented by the patient and the history elicited from him. It impresses us that a diagnostic accuracy of 94 per cent in chronic nervous exhaustion compares favorably with the accuracy of diagnosis in other conditions. However satisfying this percentage of accuracy may be, it is desirable to improve it. Our study shows that the conditions which need to be most carefully sought for, before the diagnosis of chronic nervous exhaustion is made, are hyperthyroidism, chronic encephalitis, and tuberculosis.

Errors in medical or surgical diagnosis are viewed differently. If a disease clinically diagnosed as acute appendicitis is shown at operation to be something else, the diagnosis is considered much less in error than if a patient thought to have chronic nervous exhaustion is eventually

shown to be affected with hyperthyroidism. Such discrimination is not only unfair, but it encourages the diagnosis of organic disease when none is present. Much is being said and written regarding nervous indigestion, constitutional biologic inferiority and the various types of psychoneurosis. A real service would be accomplished if the accuracy of such commonly made diagnoses can be determined.

SUMMARY

Case records of 235 patients were studied in order to determine the accuracy of the diagnosis of chronic nervous exhaustion made on an average of six and a half years before final examination of the patient. In our cases, the accuracy of the diagnosis of chronic nervous exhaustion was found to be between 85 and 98 per cent. The actual figure seems to be about 94 per cent. The figure stated indicates that the diagnosis of chronic nervous exhaustion, when made under good circumstances, is reliable in high degree.

IRRADIATION TREATMENT OF HYPERTHYROIDISM *

By GEORGE E. PFAHLER, M D , Sc D , F A C P , *Philadelphia, Pennsylvania*

THE INTERNIST is usually the first to come in contact with a case of hyperthyroidism. To him belongs the responsibility of making the diagnosis by its differentiation from other similar clinical syndromes, and he should remain in charge until the patient is restored to a normal condition and is able to carry on his usual occupation. The treatment of hyperthyroidism does not consist merely in treating the thyroid either by irradiation or operation, the predisposing and exciting causes of the disease should be removed, and after active local treatment the patient should be guided and guarded by competent medical advice. Crile,¹ says "In 33 per cent of our total cases, there is a recurrence of the hyperthyroidism after partial thyroidectomy. In every case in which this occurs it will be found that there has been a persistence of the agents which were active in producing the primary hyperthyroidism—focal infection, social maladjustments, worry, overwork or some other strain." In general, about 10 to 20 per cent of cases of hyperthyroidism fail to get permanently well, whether treated by surgery or irradiation. It is, therefore, quite proper that the subject of nonoperative treatment of hyperthyroidism should be presented before this body, for the general care of the patient is absolutely essential.

It is well known to you all that patients who are suffering from hyperthyroidism associated with a goiter postpone the consultation with their family physicians for fear that they will be sent to a surgeon for operation. To avoid such delays, and to conserve the patients' energy it is therefore well to remember that irradiation therapy is approximately of equal value to surgery in the end results, and if patients learn that not all cases must be operated upon they will be less likely to delay consultation.

In dealing with hyperthyroidism, we must assume that there is an overgrowth or a new growth of the thyroid gland, or a hyperfunction of the normal amount of glandular tissue. The condition can be relieved by surgery and satisfactory results can be obtained if the surgeon removes just the right amount of tissue, or the disease can be controlled by irradiation which gradually reduces the activity of the cells, even in cases with no tumor, hypertrophy and causes an atrophy of the hypertrophic or hyperplastic tissue when present. With careful clinical observation checked by tests of thyroid metabolism one need not exceed the necessary dosage.

INDICATIONS FOR IRRADIATION

Based upon our observations and those of other radiologists, we believe that irradiation is indicated in all cases of hyperthyroidism in which the

* Read before the American College of Surgeons, Philadelphia, September 1934.

patient is not in crisis, or is not suffering from definite pressure symptoms. We recommend operation in all simple or nontoxic goiters, unless there is some contraindication, in which case a moderate amount of irradiation may be used. Sometimes brilliant results are obtained even with large goiters of this type.

ADVANTAGES OF IRRADIATION

1 The fear of operation is eliminated and therefore the patient is more likely to come under treatment early and before cardiac damage has taken place.

2 Due to elimination of this fear, and early treatment, the patients are not interrupted in their occupation. When the disease is well advanced, or serious symptoms are present, they must, however, be put at rest.

3 There is no pain or shock and no great inconvenience if the condition is treated reasonably early.

4 Patients with advanced disease or serious heart complications may be treated without shock, and if radium is used, need not even be removed from their room.

5 There is no risk of mortality from the treatment.

6 There is an absence of scars or keloid formation.

7 The end results are approximately equal to those obtained by surgery.

OBJECTIONS

1 *Burns* The danger of burns naturally comes into a patient's mind, because they have occurred occasionally in the early years of irradiation therapy when the method was being developed and, since such patients do not die, a few such accidents in the country become known far and wide, whereas if a patient dies during an operation, from any accident or any complication, burial takes place. It is accepted as one of the hazards of the procedure and may be ignored, or is soon forgotten.

2 *Telangiectasis and skin atrophy* are dangers which must be taken into consideration. In our cases the former has occurred in 30 per cent of 533 cases, but these have occurred in our earlier treated cases. Its occurrence depends upon the amount of the total irradiation, and while it may follow a single excessive dose of rays, it may occur without any erythema ever having been produced. We have not seen telangiectasis in any cases in which we had not given more than eight series such as are described in our technic. We aim, therefore, to obtain our results with from six to eight series. Even when telangiectasis has occurred, it has been, except in one case, only slight, and has not bothered the patients much.

3 *Exacerbation of symptoms* may occur after the first treatment. This has been especially emphasized by Borak,² Pordes³ and Goette,⁴ but in our experience such an increase has been insignificant and no more than may occur from time to time independent of treatment. If such an increase is feared, it may be well to decrease the dose in the first series, especially in the severe cases.

4 *Myxedema* Myxedema has not occurred in any of our cases. Hypothyroidism has occurred only in four cases of our series, or less than 1 per cent, and in only one of these four cases was it sufficiently severe to require desiccated thyroid. Groover⁵ reported subsequent hypothyroidism in only 1.3 per cent of his cases. Our low percentage of hypothyroidism after irradiation is in part due to our ability to reduce the excessive secretion gradually, and in part due to the fact that the normal thyroid cells are rather resistant to irradiation. Walters, Anson, and Ivy⁶ state the experimental literature at hand indicates that the normal thyroid tissue is resistant to roentgen-rays and concluded from their own studies that the "normal thyroid of the dog is quite resistant to roentgen-rays and degenerative changes are not caused by the dosage used in the experiments, which is a dosage known to be of clinical value, and in the dosage used do not cause extensive proliferation of connective tissue." *We have also clinical proof that the normal thyroid is very resistant to irradiation, in the fact that we have obtained no hypothyroidism in any cases of carcinoma of the larynx, pharynx or neck in which we have used many times the total dosage used in hyperthyroidism.* The diseased thyroid tissue on the other hand seems to be very sensitive as judged by clinical results.

5 *Damage to the Parathyroids* Ivy and his associates state "The experimental results indicate that the clinical dosage in the treatment of hyperthyroidism will not injure the parathyroids." Confirming the experimental work, we can state that none of our patients and none recorded in the literature have shown any tetany following irradiation. Neither has any tetany occurred following the enormous dosage used in the treatment of carcinoma of the larynx, in which the thyroids and the parathyroids are constantly exposed to irradiation of sufficient quantity to cause the surface skin and the surface of the mucous membrane to desquamate.

6 *Difficulty in Subsequent Surgical Removal if This Should Be Necessary* This objection need only be considered in a small percentage of cases (only 0.8 per cent of our cases were operated upon), and in only one of these, an early case in our series, was any difficulty involved. It is now generally admitted that adhesions are found in as many cases which have had no previous irradiation as in cases which have been treated (G. Schwartz). Eiselberg, who was first to consider adhesions as a postirradiation complication, now disregards them as irrelevant.

7 *Slow Response to Irradiation* With irradiation we usually get some improvement at the end of a month and very definite improvement at the end of two months. If the surgeon uses two weeks preparatory to operation, two weeks to recover from the operation and a month for convalescence, the delay in time is not so great. At the end of these two months, however, we can generally expect a more complete relief of symptoms from surgery than from irradiation, because the surgeon removes the excess of glandular tissue. In contrast with irradiation we reduce the hyperactivity and the hypersecretion gradually. This is a slow and progressive effect.

This slow response is not without its advantages, however, since the activity of the gland can be checked by frequent metabolic determinations and the final result controlled with greater nicety than when the hyperfunctioning gland is removed at one sitting. During this period of early treatment the internist should use all his known methods of helping the patient.

8 Permanent Cardiac Impairment Developing during the Prolonged Irradiation Treatment The improvement from irradiation comes more slowly than from surgery, but this difference is not as great as would at first appear. There is likely to be considerable delay and advancement of the disease and damage to the heart before the patient will consent to an operation, which will make up for any delay in the results from irradiation. Progress in cardiac impairment may also occur in cases treated surgically, as is indicated by the report made by Willius⁸ from the Mayo Clinic, in which he states: "At the time of initial examination at the Mayo Clinic, auricular fibrillation was found in 7 per cent of patients with exophthalmic goiter, and in 9 per cent of patients with hyperfunctioning adenoma. These percentages are doubled while the patient is under observation, that is, during the pre-operative, operative and postoperative periods. Auricular fibrillation may occur as a permanent, intermittent or paroxysmal disorder."

Holzknicht⁹ states that not one case is found in the literature, proving that the prolonged period of irradiation resulted in unnecessary damage to the heart.

TABLE I
An Analysis of 698 Cases of Goiter *

Cases with hyperthyroidism treated with roentgen-rays	440
Cases with hyperthyroidism treated with radium	6
Nontoxic goiter cases treated	59
Malignancies of thyroid treated	28
Total cases treated	533
Simple or nontoxic goiters in which we advised against irradiation and which were not treated	165
Total	698

* These statistics have been collected from our records by my associate, Dr. Jacob H. Vastine.

Under hyperthyroidism or thyrotoxicosis we have classed all exophthalmic goiter cases, all toxic adenomas, and those which had a high basal metabolism associated with the characteristic nervous symptoms even when no goiter and no exophthalmos were present.

TABLE II
Results Obtained by Us in the Treatment of 440 Cases of Hyperthyroidism

	Cured	Markedly Improved	Not Improved
Percentage	57.3	30.6	12.1
Average number of treatments	6.1	5.7	3.7
Average time observed	6.5 yrs	2.8 yrs	
Total cured or markedly improved	87.9 per cent		

We have classed as cured those cases in which the basal metabolism is between plus 10 per cent and minus 10 per cent, the pulse has returned to normal, in which the weight has increased, approximately to what it was before the onset of toxic symptoms, and nervous and other clinical manifestations have subsided; and in which the goiter has either completely disappeared or is so involuted as to be entirely unobjectionable from a cosmetic standpoint.

We have classed as improved those cases in which the basal metabolism is within normal limits or markedly decreased, and in which all clinical signs of thyrotoxicosis have disappeared, except a residual myocardial deficiency, which was present before the beginning of irradiation. We have classed here also those inoperable cases given irradiation to reduce the toxicity and prepare them for operation. The nomenclature frequently used by the internists and surgeons is "economic restitution" or "rehabilitation." In our series it can be seen that in 87.9 per cent of the cases "economic restitution" or "rehabilitation" was obtained.

RECURRENCE

Among patients we regarded as cured there were only two post-irradiation recurrences, or less than 1 per cent. There were cases in which the metabolic rate was rapidly brought down to within normal limits and subsequent tests within several months showed it to have risen 5 or more per cent above normal. In such cases which had been insufficiently treated, one or two more series of treatments were necessary before stabilization of the metabolic rate permanently within normal limits was obtained. These were not regarded as recurrences, since the patients were really still under treatment.

HYPERTHYROIDISM WITHOUT PALPABLE GLANDULAR ENLARGEMENT

This is a class of cases in which irradiation is particularly indicated. There were 37 of these cases in our series. There was economic restitution in 29. The treatment failed in five cases and three patients could not be treated.

In three cases which were not responding satisfactorily, we tried treatment over the cervical sympathetic ganglia and over the suprarenals but with appreciable effects.

If it does not develop, because the larynx and arytenoids were protected. Four of our earlier cases developed a severe tracheitis, but these were not more than the eight series, and it was doubtful whether the effects were due to the irradiation.

No evidence of injury to the parathyroid glands was observed in any of the cases. It is likely that the normal parathyroids, like the normal thyroid, are not injured by irradiation. We believe, however, that a diseased parathyroid gland may be injured. A contributory clinical observation has been made by Dr. J. H. Merriam.

TECHNIC

We routinely employ roentgen-rays, using 130 kilovolts, 5 milliamperes, at 25 to 30 centimeters distance, with the equivalent of 6 millimeters of aluminum filtration. The cervical region is divided into four fields, approximately 5 by 15 centimeters in size. Two of these are anterior and two are posterolateral. The lower border extends down over the thymic region. The larynx is protected with lead. The rays are directed medially and downward, so that a cross-firing effect is obtained in the thyroid region. These four areas constitute one series and they are usually given in one day, repeating this series in three weeks, then in four weeks, increasing the interval according to the improvement obtained. In simple or colloid goiters, 30 or 40 per cent doses may be given through the four above fields without danger of producing hypothyroidism. These several small doses will often be sufficient to show a definite decrease in size. In adenomata, localized doses are usually employed, cross-firing the adenoma through two portals.

In the mildly toxic cases we give an initial 50 per cent skin erythema dose through each of four portals. This is repeated in three weeks and then the amount is decreased and the interval increased. In the severer cases it is better to begin with smaller doses, not exceeding 40 per cent at the first series. This may be increased at subsequent series. More than six series are rarely necessary, a good response sometimes being seen after four series. We are reluctant to give more than six or eight series. If a patient is not definitely improved after three to five series, and a lapse of two or three months from the beginning, other measures should be employed. A careful record of the patient's pulse, weight, and general health and the condition of the skin is made at each visit and frequent metabolic determinations are made. Foci of infection are removed. Chest examinations are made routinely on each new patient. We recommend administration of quinine hydrobromide in five to ten grain doses, three times a day, unless ringing of the ears occurs (Bram). Dodd's lotion is prescribed for application to the neck to avoid skin damage. The patient is cautioned against sunburning the neck or applying irritating salves or lotions. Rest, so far as practicable, is advised, the patient being told never to stand when she can sit and never to sit when she can lie down. A high caloric diet of easily digested food is recommended. The patient is advised against the use of stimulants. We have not found the administration of iodine helpful.

We employ roentgen irradiation routinely, because it has produced such uniformly good results. We have treated only a few cases with radium which were unsuitable for roentgen-ray treatment. Loucks¹¹ and Ginsburg¹² prefer radium and have obtained excellent results. Surely as good results can be obtained with radium as with roentgen-rays. It would seem that radium is preferable for patients who cannot come for treatment, or for whom the excitement caused by the machinery would be harmful. We have successfully used radium needles, interstitially, in a localized adenoma.

which did not respond to roentgen therapy as fast as we felt it should. This can be done under mild narcosis without shock to the patient and has proved to be a valuable procedure in selected cases.

RESULTS OBTAINED BY OTHER RADIOLOGISTS

Our results closely parallel those of other radiologists. In a previous presentation we reviewed the reports of 20 other radiologists, covering over 3300 cases, of which an average of 85 to 90 per cent have been cured or markedly improved. There have been several excellent reports upon this subject since that time. That of Menville¹³ is probably the most comprehensive and the most representative, since he reviewed the work of 75 radiologists, both in Canada and the United States, by sending questionnaires. This report covered 10,541 cases treated by irradiation, of which 66.2 per cent were cured, 21 per cent were markedly improved and 12.4 per cent were not improved. It is interesting to note that 10 per cent of these 10,541 were cases in which surgery had previously been tried without success. There were 8.45 per cent of recurrences following irradiation. These results, which are a fairly accurate cross-section of the work done by radiologists generally, compare favorably with the cross-section of the work done by the average surgeon as reported by MacLean¹⁴ in which he found the operative mortality rate alone to be 7 per cent in cases of exophthalmic goiter treated surgically, although the best clinics report less than 1 per cent.

BRIEF REPORTS OF CASES HAVING NO DEFINITE THYROID ENLARGEMENT

It is impractical in a paper of this kind to make a detailed record of all cases. Probably the most interesting and most difficult cases for diagnosis are those in which there is no definite palpable thyroid enlargement, or in other words, no goiter. Hamburger and Lev,¹⁵ in 1930, have reported a series of such cases and again called attention to the difficulty of making a diagnosis of hyperthyroidism in the absence of goiter and in the absence of other typical symptoms. They referred to the fact that Charcot¹⁶ recognized this difficulty in 1885, and Chvostek¹⁷ also in 1887. Further studies were also made on this group of cases by Levine and Sturgis,¹⁸ and Priest¹⁹ and Tucker.²⁰ It is this group of cases that are particularly liable to be overlooked and mistreated for a long time. It is also this group of cases which are probably less favorable for operation. We are likely to see more of this class of patients, because of the fact that no goiter can be felt, and they are therefore referred to radiologists for treatment. I am, therefore, recording very briefly in chronological order, our cases which had no definite thyroid enlargement, as they have been collected from my office records for me by Dr. Jacob H. Vastine. Those patients, referred for treatment, had been studied and diagnosed by eminent clinicians whose diagnosis I am giving as the best that could be made.

CASE I

Miss M K, age 19, was referred for treatment of exophthalmic goiter on April 5, 1913. The patient developed this condition after an attack of influenza in December 1912, after which she became extremely nervous, and had a rapid pulse. She was weak. Her eyes were strikingly prominent, and while she had some general fullness of the neck, there was no palpable goiter, or definite localized enlargement. Her general appearance, however, was that of a typical exophthalmic goiter. She was given fractional doses of roentgen-ray treatment, which was the custom at that time, between May 5, 1913 and June 26, 1913. On October 7, 1914, she was free from all symptoms, except the prominence of her eyes. She has remained free from symptoms, except for the eyes, which have not yet returned to normal, though they have shown marked improvement. Since then, she has been married. She was in an airplane accident in 1928, after which her nervousness increased somewhat, but an examination on October 5, 1929 showed no evidence of goiter, and only slight exophthalmos. Her skin was normal, her weight 147 lbs, her pulse at rest 78, and after exercise 84. She was reported well on January 13, 1933.

CASE II

Miss A R, age 28, referred on May 28, 1918, by Dr L N Boston, of Philadelphia, for treatment of hyperthyroidism. Exophthalmos had been present about six years, and one and a half years previously both thyroid arteries had been ligated by Dr A C Wood. There was no enlargement of the thyroid. She improved temporarily after the ligation. She was brought for treatment on a stretcher. Her pulse was 136 while lying down. She was extremely nervous. She showed definite improvement after the first treatment, and after four treatments, she was able to sit up for three hours at a time, and could walk a distance of a city block without resting. In April 1919, she returned to work in a knitting mill. She was given eleven treatments in all, during a period of eleven months. On January 28, 1929, her pulse was 68 at rest, and 78 after exercise.

CASE III

Mrs E S, age 25, was referred on April 30, 1919, by Dr Wm H Good, of Philadelphia, for treatment of hyperthyroidism associated with exophthalmos, but without any enlargement of the thyroid gland. At rest, her pulse was 80, but after slight exertion, was 120. We gave four series of treatments with the roentgen-ray during a period of three months, after which her nervous symptoms had definitely improved. She was reported entirely well by Dr Good on July 14, 1929, or approximately ten years after beginning treatment.

CASE IV

Mrs F E, age 32, was referred for treatment of hyperthyroidism by Dr C M Fish, of Pleasantville, N J, on May 25, 1920. Four years previously she developed a profound and unexplained asthenia, and she began to feel tired without doing anything. It even made her tired to go downhill. During the year prior to treatment, she had had a persistent tremor. She had been treated during a year and a half for rapid heart by Dr Carrington of Atlantic City. She then entered the University of Pennsylvania Hospital, March 1, 1920, under the care of Dr H M Fussel who made a diagnosis of hyperthyroidism. She rested in bed for several weeks. The basal metabolic rate was plus 15. There was no palpable goiter, and no exophthalmos. She suffered from attacks of diarrhea. Dr Fussel advised ligation of the thyroid artery. An abnormal shadow was shown by the roentgen-rays in the upper mediastinum which probably was an enlarged aberrant thyroid. She showed some improvement from rest in bed before coming to me. At the beginning of roentgen-ray treatment, the

pulse was 120. On January 7, 1921, all her symptoms had disappeared, and she was apparently well. She was given six series of roentgen-ray treatments between March 25, 1920 and October 29, 1920. The basal metabolic rate in July 1931 was plus 6. On March 20, 1933, her pulse on arrival was 80, after exercise it arose to 90. At this time, her hyperthyroid symptoms seemed to have entirely disappeared.

CASE V

Mr. A. T. B., age 39, referred by Dr. T. E. Wills of Pottstown, Pa. on June 30, 1920, for roentgentherapy for hyperthyroidism. During six months, he had little or no enlargement of the thyroid, but he had tremors, nervousness, palpitation, loss of weight, and tachycardia. Roentgen-ray examination showed a substernal thyroid enlargement. Under roentgen-ray treatment, all of his symptoms disappeared, and on October 6, his pulse was 78 after exertion, and he was practically free from symptoms. On December 17, 1920, he was completely free from symptoms. Dr. Wills reported him well on January 26, 1933.

CASE VI

Mrs. M. W. was referred by Dr. A. F. Collier, of Waterbury, Conn., for treatment of hyperthyroidism on January 31, 1921. Her previous treatment had consisted of rest and iodine treatment which gave some temporary improvement, but the symptoms recurred, and there was no improvement during a period of six months. The symptoms consisted of nervousness, excitability, palpitation, exhaustion, loss of weight, and some exophthalmos. The thyroid was not enlarged. The patient was given nine series of roentgen-ray treatments between January 31, 1921 and May 17, 1922. There was improvement after the first treatment, and at the time of the last treatment, her pulse was 90 as compared with 140, her weight was 153 as compared with 131, her basal metabolic rate was plus 3.

CASE VII

Miss F. P., age 28, was referred on account of hyperthyroidism, with no palpable goiter, on March 30, 1921, by Dr. E. H. Goodman, and Dr. John H. Musser of Philadelphia. The basal metabolic test showed plus 24. Her pulse rate was 136. Roentgen-ray examination showed no enlargement of the thyroid. The heart action fluoroscopically was very excitable. An examination of the eyes showed some congestion in the left eye, but no exophthalmos, and nothing else abnormal. Roentgen-ray examination of the pituitary showed some calcareous deposit in the region of the sella. After her second series of treatments, she felt very much better. She was less nervous, but still had some of the former vague fullness and distress at the back of the head, which, however, was less pronounced. Her pulse had dropped to 100. The last series was given October 20, 1921, at which time she seemed to be very much better from her symptoms. However, she developed some new symptoms in December and was referred to Dr. Francis D. Price by Dr. Goodman for operation upon the thyroid. She was called on October 12, 1922 for an examination of her spine on account of some pains. The roentgen-ray examination showed hypertrophic osteoarthritis, and at the time her hyperthyroid symptoms had returned even after the operation. She was too nervous to permit a roentgen-ray examination of her thyroid, and the operation failed to cure her, but it was also a surgical failure.

CASE VIII

Mr. H. B. was in care of his own record on May 1, 1921. He had been diagnosed as hyperthyroidism by Dr. E. H. Goodman on December 19, 1919 with a diagnosis of toxic goiter, and was treated by Dr. Goodman with iodine and roentgen-ray treatments except that he got no roentgen-ray treatment. He was referred to Dr. C. C. C. of Columbia

Ohio, had seen the patient and had made a diagnosis of hyperthyroidism. He found no enlargement of the thyroid. The duration of his symptoms was 18 months. He suffered from nervousness, sweating, loss of weight, tremor, and exophthalmos. He received four series of roentgen-ray treatments from May 4, 1921 to August 11, 1921, at which time his symptoms had disappeared. On January 9, 1933, the patient reported "General health good. No other treatment. Pulse after rest 70, pulse after exercise 86. Weight 137 in the nude. Neck normal. Eyes normal."

CASE IX

Mrs. H. M., age 24, was referred on May 7, 1921 by Dr. Andrew Jackson, of Waterbury, Conn., for roentgentherapy of hyperthyroidism which had followed pregnancy two years previously. She had developed a rapid heart, a general nervous condition, and loss of weight, but she had no exophthalmos, and no enlarged thyroid. The cardiac action had the excitability as seen fluoroscopically which is characteristic of what one finds usually in hyperthyroid cases, and which, while probably not pathognomonic, at least always makes me think of hyperthyroidism. Her pulse at rest was 104, and after exercise 130. This abnormal increase in pulse rate with slight exercise seems to run parallel with the basal metabolism as determined in more recent years. She was given nine series of roentgen-ray treatments between May 7, 1921 and February 18, 1922, and on this date, a basal metabolism test was made which was minus one. She had increased in weight from 113.5 to 135 lbs. All of her other symptoms had disappeared. She was reported well January 31, 1933.

CASE X

Mrs. J. S., age 33, was referred by Dr. Andrew Jackson, of Waterbury, Conn. on May 21, 1921, with the diagnosis of hyperthyroidism. She had been nervous for many months, but one month before coming to me, she had difficulty in swallowing, a feeling of suffocation, and a constant oppression in the throat. This led to a suspicion of a goiter, but Dr. Jackson and I were unable to palpate a goiter. On the basis of loss of weight, tachycardia, and her general nervous condition, he made a diagnosis of hyperthyroidism. I was unable to palpate any enlarged thyroid, but by roentgen-ray examination, I found a compression of the trachea, and a diagnosis of substernal thyroid was made. Five series of roentgen-ray treatments were given between May 21, 1921, and November 25, 1921, at which time her symptoms were relieved, she looked well, felt fine, and her pulse had returned to normal.

CASE XI

Miss V. E., age 29, was referred by Dr. T. H. Weisenburg, of Philadelphia, for treatment of hyperthyroidism, on June 29, 1921. Previously she had had a double ligation in June 1916 and thyroidectomy in 1917. Before coming to us she had been suffering from toxic symptoms and had been bedfast for six months. She had definite exophthalmos but no palpable thyroid. She was given four series of roentgen-ray treatments between June 29, 1921 and October 12, 1921, at which time she was free from symptoms and was delighted. She immediately took up training as a technician under me. She completed this course as roentgen-ray technician, and then served as an assistant technician for an additional year in our hospital when she left to accept a position in another hospital. Her present address has been lost.

CASE XII

Miss M. L. O., age 49, was referred by Dr. Judson Daland of Philadelphia, on April 29, 1922, for treatment of exophthalmic goiter, of about one year's duration. The thyroid, however, was not enlarged. She had nervousness, irritability, sweating, dyspnea, palpitation, and loss of weight, associated with tremor and exophthalmos.

Her basal metabolic rate was plus 40. She was given nine series of treatments and on April 16, 1923, Dr. Alex. Klein wrote as follows: "This patient was referred to me by Dr. Daland in May of last year and has been under my care since. Her basal metabolism at that time was plus 40, pulse 90, respiration 24, systolic blood pressure 155, diastolic 100. A second test on November 27, 1922, shows a basal metabolism of plus 30, pulse 92, respiration 28, systolic pressure 160, diastolic 100. A test made two days ago showed a basal metabolism of plus 7, pulse 62, respiration 19, systolic pressure 170; diastolic 110. The basal rate is normal. This very marked improvement is due entirely to roentgen-ray treatment. The increasing hypertension is most probably a result of her menopause." On May 22, 1933, this patient called for inspection and was entirely well. Her pulse was 68, and her weight 153.

CASE XIII

Miss F. J. H., age 39, was referred for roentgen-ray treatment on account of hyperthyroidism on November 2, 1922 by Dr. Julian Adair, of Wilmington, Del. She was highly nervous and would break down when she attempted to do a full day's work of eight hours. She had not been able to work for five months. She had sweats, diarrhea, irritability, palpitation, tremor, but no goiter and no exophthalmos. She had a wild excited appearance. Her basal metabolic rate was plus 45. The pulse rate during rest was 130, after exercise 150. She was given the first series of roentgen-ray treatments on November 3, 1922. The second series was interfered with by an automobile accident and therefore could not be given until December 8, 1922. On August 5, 1929, the patient was symptomatically well. Her pulse was normal.

CASE XIV

Mrs. W. H., age 47, was referred by Dr. Edwin H. Johnson, of Naugatuck, Conn., on May 9, 1923 for treatment of exophthalmic goiter. Her eyes had always been prominent, but during the previous 18 months this prominence had definitely increased. She had the appearance of being extremely nervous, she was irritable and had sweating of the skin, asthenia, and tachycardia. Her pulse was 140, her basal metabolic rate was plus 21. We could find no enlargement of the thyroid. She had eight series of roentgen-ray treatments between May 9, 1923 and April 6, 1924. Her basal metabolic rate on December 18, 1924 was plus two. The exophthalmos persisted until July 1, 1929, at which time she was in other respects well.

CASE XV

Mr. H. A. D., age 54, was referred for treatment of hyperthyroidism by Dr. M. Alexander, of Waterbury, Conn., on August 15, 1923. The duration of his symptoms was three years, but they had been worse during the previous year. They consisted of nervousness, definite exophthalmos, loss of weight, without enlargement of the thyroid but with asthenia, marked tremor and a pulse varying between 100 and 140. The following note was made by Dr. Alexander on July 31, 1923. "I examined Mr. D. very carefully and came to some very definite conclusions. The symptoms are not from Graves' disease, but his case presents features which make thyroidectomy a contraindicated operation. First, his thyroid gland is not enlarged. Second, his case is not due to poisons in the system, elaborated by the thyroid, but is due to a disturbance of internal secretion. Removal of the thyroid gland is not a part of the trouble. Since the thyroid is not enlarged, removal is more difficult, and the result, less certain. We must therefore consider the condition of his heart, which is really far from normal. The heart is not enlarged, but it is in operation with impunity." On August 31, 1923, his pulse was 122. Fluoroscopic examination of the heart showed enlargement of the right ventricle, but the heart showed enlargement of

both the right and left chambers. An electrocardiogram showed evidence of left preponderance and a heart rate of 130. He was given two series of roentgen-ray treatments, the second one September 13, 1923. The trip, however, was so exhausting and he was in such serious condition that we hesitated to give him further treatment. We advised treatment nearer home. On December 8, 1923, we received the following letter from Dr. Alexander: "Sorry to report that the patient died two weeks ago. The terminal illness was cardiac decompensation and hypostatic congestion of the kidneys. It is really no wonder that he died since he was in such an extremely poor condition when I sent him to you. You will please recall that I saw him only a few days before sending him to you." (Marked as a failure.)

CASE XVI

Mrs. W. H., age 64, referred by Dr. G. M. Piersol, of Philadelphia, on March 28, 1924, for treatment of hyperthyroidism. The basal metabolic rate was plus 60. She was extremely nervous and at times had diarrhea. She had lost about 40 pounds of weight and suffered from asthenia and tachycardia. Her pulse varied between 110 and 140. There was no palpable goiter, and no exophthalmos. She received eight roentgen-ray treatments between March 28, 1924, and December 16, 1924. Her basal metabolic rate on February 17, 1925, showed plus 5, and she was free from symptoms. She was still well on June 25, 1929.

CASE XVII

Mr. C. P., age 35, was referred for treatment of hyperthyroidism on November 20, 1924, by Dr. T. H. Weisenburg, of Philadelphia, at which time the basal metabolic rate was plus 48. There was a history of toxic symptoms during two to three years, consisting of nervousness, irritability, sweating, tachycardia, asthenia, and associated with hallucinations. There was no enlargement of the thyroid. The patient received only one series of roentgen-ray treatments. Then he moved to New York and later to Europe. According to the last report on January 19, 1933 his general health was fair. He had no other form of treatment. (Marked as a failure.)

CASE XVIII

Miss B. C., age 22, was referred for treatment of hyperthyroidism by Dr. Marika Lambich, of Chester, Pennsylvania on December 3, 1924, at which time her basal metabolic rate was plus 18, and her pulse 110. Her symptoms had existed since July 1924. She was markedly nervous, irritable, had abnormal sweating, and palpitation of the heart. There was no palpable thyroid, but there seemed to be an enlargement of the upper mediastinal shadow, suggesting a substernal thyroid. The cardiac action was of the type that one sees in hyperthyroidism as shown fluoroscopically. She was given six series of roentgen-ray treatments, and on June 22, 1924 she was free from symptoms and her basal metabolic rate was zero. Her basal metabolic rate on July 9, 1931 was plus 6. She was well on February 17, 1932.

CASE XIX

Mrs. H. W., age 68, was referred on April 25, 1925 by Dr. Gordon Saxon and Dr. Earl French, of Philadelphia, for treatment of hyperthyroidism associated with cardiac dilatation. The patient had a rapid pulse, weakness, and nervousness, but no enlargement of the thyroid, and no prominence of the eyes. She had marked tachycardia, with a pulse of 134 when at rest, and 160 after exercise, associated with the peculiar cardiac action as seen fluoroscopically which one finds in hyperthyroidism, and which often leads us to suspect hyperthyroidism. The roentgen examination of the chest showed a strong suggestion of enlargement of the middle lobe of the thyroid downward, but there was no palpable enlargement. The cardiac shadow was in-

creased. We gave her four series of roentgen-ray treatments between April 25, 1925 and September 12, 1925, at which time she was markedly improved, and Dr. French reported on July 22, 1929 that the patient was well. He regarded this as a remarkable cure.

CASE XX

Mrs. M. H. H., age 62, was referred by Dr. Wm. S. Bertolet of Reading, Pennsylvania on September 19, 1925. She had, however, been treated about 10 years previously at the Medico-Chirurgical Hospital for exophthalmic goiter. Her chief complaints were tachycardia, slight exophthalmos, and extreme nervousness, loss of weight, palpitation of the heart. Her pulse was 140, and her basal metabolism was plus 47. We gave her nine series of roentgen-ray treatments between September 19, 1925 and June 8, 1926, at which time her pulse had returned to normal. Her nervousness had disappeared. Her weight had returned to normal. She was seen on May 16, 1927, when she appeared well. When seen on February 26, 1932, her pulse was normal, 76 at rest, and 84 after exercise. On February 26, 1932, she was well, working regularly as a teacher.

CASE XXI

Miss F. M. B., age 44, was referred for treatment of hyperthyroidism on October 29, 1925, by Dr. H. M. Eberhard, of Philadelphia. The basal metabolic rate determined on October 27, 1925, was plus 36. She had been treated in the Woman's Homeopathic Hospital for a nervous breakdown two years previously. She was kept at rest in bed for one month and this was followed by improvement. One of her chief complaints was a "dizziness confined to the left side of the head and left side of the body." In addition to this, she complained of nervousness, irritability, sweating, palpitation and a rapid pulse. She had no thyroid enlargement. We gave her three series of roentgen-ray treatments between October 29, 1925, and December 31, 1925, at which time she seemed to be well. The basal metabolic rate on December 27, 1925 was minus 3. She was reported well by Dr. Eberhard on July 16, 1929.

CASE XXII

Mrs. W. P. N., age 39, was referred by Dr. Gordon Saxon, of Philadelphia, April 20, 1926. Her basal metabolic rate was plus 68. The duration of symptoms was six months. Her chief symptoms were nervousness, dyspnea, palpitation, sweating, loss of weight, and marked tremor. There was no thyroid enlargement. The patient even failed in appearance. Her pulse varied between 128 and 150. She was given seven series of roentgen-ray treatments between April 20, 1926, and November 15, 1926, at which time, she seemed to be well. On January 27, 1927, Dr. Saxon did a basal metabolism which showed plus 10. Her weight had increased from 104 to 124. Her pulse had dropped from 150 to 92. The basal metabolism record in her case is as follows: April 20, 1926, plus 68, June 5, 1926, plus 25, September 7, 1926, plus 19, January 27, 1927, plus 10, February 12, 1932, plus 1. She was reported well on February 20, 1933.

CASE XXIII

Miss M. L., age 47, was referred by Dr. Carl F. Welden, of Bethlehem, Pennsylvania, on January 7, 1927, for roentgen-ray treatment of hyperthyroidism. Her chief complaints were nervousness, tachycardia, and loss of weight. Her basal metabolism was plus 40. The pulse at rest was 126, after exercise 143. According to the patient's statement, her pulse went as high as 200. She had no appreciable enlargement of the thyroid gland, but she had tachycardia, a thymia, loss of weight, and nervousness. We gave her seven series of treatments between September 7, 1927, and January 20, 1928, at which time her pulse had returned to normal and her weight had

On February 29, 1932, her pulse was 76 at rest, and 82 after exercise. She had gained 27 pounds.

CASE XXIV

Mrs R C, age 31, was referred for treatment of hyperthyroidism by Dr Clifford Waas, of Atlantic City, N J, on April 25, 1928. Her symptoms had extended over a period of a year and a half, consisting of nervousness, irritability, palpitation, loss of weight, dyspnea, and tremor. Her basal metabolic rate was plus 16, on April 25, 1928. I was unable to find any enlargement of the thyroid by roentgen-ray examination or palpation, and no exophthalmos. She had two series of roentgen-ray treatments April 25, and May 16. When examined on July 20, 1929, she was free from any symptoms, had gained 15 pounds in weight and seemed to be in perfect health. She was reported well on January 5, 1933.

CASE XXV

Miss T B, age 48, was referred by Dr Francis Dever, of Bethlehem, Pennsylvania on May 14, 1928, for treatment of hyperthyroidism. She had extreme nervousness during three months with loss of 40 pounds in weight. She suffered with marked tremor, excitability, and had a pulse rate of 145. She had no goiter, and no exophthalmos. Her basal metabolic rate was plus 40. She was given six series of roentgen-ray treatments between May 14, 1928, and October 2, 1928, at which time she was free from symptoms, and had gained 15 pounds in weight. Her pulse at rest was 88, and after exercise 98. Her basal metabolic rate was minus 7. She was well July 10, 1929.

CASE XXVI

Mr C S H, age 45, was referred by Dr J M Anders and Dr John H Dripps, of Philadelphia, on June 2, 1928. There was a history of thyroid enlargement since February 19, 1928, but at the time the patient came to us there was no palpable enlargement. There was no exophthalmos. He had lost 27 pounds in six weeks, had marked tremor, was very irritable, suffered from dyspnea, palpitation, diarrhea, and the basal metabolic rate was plus 97. This patient came for only one treatment and was then operated upon by Dr Charles Frazier in July and in October 1928. (Marked as a failure.)

CASE XXVII

Miss M P, age 19, was referred for treatment of hyperthyroidism by Dr Horace Ewing, of Philadelphia, on July 12, 1928. Her chief symptoms were loss of weight, nervousness, asthenia, and a basal metabolic rate of plus 58. Her pulse rate at rest was 104, and after exercise 120. The patient improved after the first treatment but came only for one more. The final result is unknown. She cannot be traced.

CASE XXVIII

Mrs W B F, age 46, was referred for treatment for exophthalmic goiter, on March 18, 1929, by Dr Thomas Klein, of Philadelphia. The patient had a thyroidectomy done four and three-fourths years previously, and also had had a few roentgen-ray treatments, following which she felt fairly well for one year, and then became nervous again, lost weight, and developed an exophthalmos of the left eye. She had the appearance of being poorly nourished, and had a noticeable exophthalmos of the left eye. Her basal metabolic rate was plus 35. The patient had two series of roentgen-rays (added to that already received before coming to us) on March 18, 1929, and April 10, 1929. She has had no treatment since, because the last treatment given to her gave some symptoms of indigestion which she blamed on the treatment, and therefore, she was unwilling to have more. On January 16, 1933, her weight had increased two pounds, her neck was normal, and her eyes were normal, but her pulse was still

120 She had insufficient treatment, but there seemed to be some improvement as a result of the treatment she had received (Marked as a failure)

CASE XXIX

Mrs. H. S., age 43, was referred for treatment of hyperthyroidism by Dr. Myrtle Frank, of Egg Harbor, N. J., on March 27, 1929. The patient had only one treatment. She had symptoms of nervousness, but no palpable thyroid enlargement. She had irritability, palpitation, dyspnea, and no exophthalmos. She complained of tremor and sweating. Her basal metabolic rate was plus 20. She could not be traced.

CASE XXX

Mrs. A. J. S., age 32, was referred for treatment of hyperthyroidism on December 2, 1929, by Dr. F. A. Faught, of Philadelphia. Her chief complaint was nervousness, loss of 38 pounds in weight, asthenia, headaches, pain in the back of the head and neck intermittently. There was doubtful bilateral enlargement of the thyroid. She complained of some palpitation, but no exophthalmos. She had slight tremor. Her basal metabolic rate was plus 20. The patient received five series of roentgen-ray treatments between December 2, 1929 and May 19, 1930, when the basal metabolic rate was plus 7, the pulse 82, and her general health improved. Her basal metabolic rate in March 1931 was minus 4. She had no fullness in the neck, and her eyes were normal.

CASE XXXI

Miss E. B. B., age 23, a stenographer, was referred on February 19, 1930, by Dr. L. W. Pangburn, of Philadelphia, for treatment of hyperthyroidism. During six months, she had complained of extreme nervousness, irritability, sweating, asthenia, loss of weight, and palpitation. Her eyes were very prominent, her pulse was 120. Fluoroscopically, the heart action showed the excited action which always suggests hyperthyroidism. No goiter was palpable, and no goiter was demonstrated by roentgen examination. Her basal metabolic rate was plus 15. She was given three series of roentgen-ray treatments between February 19, 1930, and April 10, 1930. The basal metabolic rate on June 5, 1930, was plus 3. Her pulse was normal, but her eyes were still slightly prominent. On January 18, 1933, she was well.

CASE XXXII

Miss L. G., age 21, was referred for treatment of hyperthyroidism by Dr. L. F. Faught, of Philadelphia, on March 28, 1930. In December 1927, she had a basal metabolic rate of plus 4. In December 1929, she developed definite symptoms of hyperthyroidism and her basal metabolic rate was plus 11. Under iodine treatment, it fell to plus 13 on February 6, 1931. On March 3, 1930, her basal metabolic rate was plus 21. Her chief complaints were "peculiar waves" passing over the face, especially in her face, and other times in localized areas through her body. In addition to the nervous symptoms, she had tachycardia and asthenia. There was no enlargement of the eyes, no enlargement of the thyroid. We made a roentgen examination but could recognize no substernal enlargement, and no enlargement of the neck. The roentgen examination showed an enlarged thyroid. Her basal metabolic rate on June 12, 1930, was plus 10. She received seven series of roentgen-ray treatments between February 19, 1930, and June 12, 1930, when she seemed to be symptomatically well. On July 25, 1930, her basal metabolic rate was plus 2. She was reported "well" on August 1, 1930.

CASE XXXIII

Miss L. G., age 21, was referred on April 15, 1930, by Dr. Francis J. Faught, of Philadelphia, for treatment of hyperthyroidism. Her basal metabolic

rate was plus 42 The patient had exophthalmos and some general fullness of the neck, but no goiter He had seven series of roentgen-ray treatments between April 15, 1930 and October 27, 1930 He was not responding well Therefore, treatment was given on December 8, 16, 27, and 30, 1930, over the suprarenals The basal metabolic rate dropped to plus 26, but he was not well The patient was operated upon on April 30, 1931 There has remained some prominence of the eyes, but otherwise the patient has recovered (Marked as a failure)

CASE XXXIV

Miss A S K, age 38, librarian, was referred for treatment of hyperthyroidism by Dr Gordon Saxon of Philadelphia, on May 16, 1930 At that time her basal metabolic rate was plus 74 This condition developed after an attack of influenza in January 1930 Her chief symptoms were nervousness, irritability, palpitation, asthenia, dyspnea and loss of weight There was no enlarged thyroid, and no prominence of the eyeballs Her pulse rate was 126 She was given eight series of roentgen-ray treatments between May 16 1930 and January 30, 1931 Her basal metabolic rate on January 30, 1931, was plus 33 On September 19, 1931, it was plus 28 and on March 21, 1932, it was plus 10

CASE XXXV

Mr C E W, age 57, was referred for treatment of hyperthyroidism by Dr Francis J Dever, of Bethlehem, on November 29, 1930 He was suffering from exophthalmos, tickling sensation in the throat, marked nervousness, irritability, palpitation, sweating, loss of weight, and tremor He had a basal metabolic rate of plus 70, with no enlargement of the thyroid He improved clinically, but not sufficiently His basal metabolism did not improve It was still plus 71 on May 13, 1931 He was, therefore, operated upon by Dr Wm L Estes, Jr, who did a subtotal thyroidectomy, after which he recovered except for the prominence of his eyes (Marked as a failure)

CASE XXXVI

Mrs J B, age 61, was referred for treatment of hyperthyroidism by Dr Gordon Saxon, of Philadelphia on November 2, 1931 The duration of her symptoms was seven months They consisted of nervousness, asthenia, palpitation, and loss of about 32 pounds of weight She had tachycardia with a pulse rate at rest of 140 and after exertion of 156 Her basal metabolic rate was plus 33 She also had a marked tremor Roentgen-ray examination of the chest seemed to show some increased sub-sternal shadow above the arch of the aorta, which might be due to enlarged thyroid, but there was no palpable thyroid enlargement and no exophthalmos We gave her three series of roentgen-ray treatments between November 2, 1931 and January 4, 1932 On June 13, 1933, she was reported as being entirely well by Dr Saxon

CASE XXXVII

Mrs T M, age 35, was referred by Dr Gordon Saxon, and Dr William Higbee, of Philadelphia, on May 27, 1932, for treatment of hyperthyroidism The patient had had a thyroidectomy on March 19, 1927 During the year before coming to us, she was extremely nervous, irritable, had palpitation, asthenia, sweating, loss of weight, occasional diarrhea, and tachycardia Her basal metabolic rate was plus 13 The patient received four series of roentgen-ray treatments between May 27, 1932 and July 17, 1932, at which time she had shown marked improvement, the pulse rate being approximately normal and her weight having increased The basal metabolic rate on October 8, 1932, showed minus 20 At that time her pulse was 72, and she was practically symptom free

SUMMARY AND CONCLUSIONS

1 Irradiation with either roentgen-rays or radium may be accepted as a useful method of treatment of hyperthyroidism, since the end results are approximately equal to those obtained by surgery

2 The fear of operation or delays preceding operation are likely to lead to cardiac impairment. This delay can be eliminated by the use of irradiation therapy.

3. Irradiation therapy involves no pain, shock or great inconvenience

4 Associated medical care and general directions for the conservation of energy are essential

REFERENCES

- 1 CHILF, G. W. The treatment of certain types of hyperthyroidism, Transactions of the American Association for the Study of Goiter, 1932, p. 1-10
- 2 BORAVK, J. Die Röntgentherapie und die Organotherapie bei innersekretorischen Erkrankungen, II. Die Ovarien, Strahlentherapie, 1925, xvi, 441-478
- 3 POWERS, F. Die oligosymptomatischen Thyreotoxikosen und deren Röntgenbehandlung, Strahlentherapie, 1928, xxv, 619-633
- 4 GOETTER, K. Über Schädigung nach Bestrahlung von Morbus Basedowni, Fortschr. a. d. Geb. d. Röntgenstrahlen, 1929, xxxix, 111-113
- 5 GPOOPER, T. A. and others. Roentgen irradiation in treatment of hyperthyroidism, statistical evaluation based on 305 cases, Jr. Am. Med. Assoc., 1929, xcii, 1730-1734
- 6 WATKINS, O. M., ANSO, B. J., and IVEY, A. C. Effect of x-rays on thyroid and parathyroid glands. Radiology, 1931, xvi, 52-58
- 7 SCHWARTZ, G. Über die Röntgentherapie des Basedowschen Krankheit, Strahlentherapie, 1932, xliii, 349-356
- 8 WATKINS, I. A. Heart in thyroid disease, Ann. Clin. Med., 1923, i, 269
- 9 HILF, ROBERT. Über die Röntgentherapie der Basedowschen Krankheit, Strahlentherapie, 1928, xxx, 605-612
- 10 MURPHY, F. A. Irradiation of parathyroids in cystic disease of bones, Jr. Am. Med. Assoc., 1932, xcvi, 1733-1734
- 11 FOLGER, R. E. Clinical evidence of thyrotoxic control after radium therapy, Am. Jr. Roentgenology, 1927, xviii, 509-512
- 12 FOLGER, R. E. Value and place of radium in treatment of disease of thyroid gland, Am. Jr. Roentgenology, 1930, xxi, 283-297
- 13 MURPHY, F. A. Radiologic aspect of thyrotoxicosis, Radiology, 1932, xviii, 568-575
- 14 MURPHY, F. A. Treatment of goiter, III, Med. Jr., 1925, xlvii, 354-358
- 15 FOLGER, R. E., WATKINS, O. M., and IVEY, M. W. Masked hyperthyroidism, Jr. Am. Med. Assoc., 1931, xciv, 2574-2576
- 16 FOLGER, R. E. and MURPHY, F. A. (Contre exophthalmique), formes frustes, nouveau signe, Bull. Soc. Med. Paris, 1885, 68, 113
- 17 FOLGER, R. E. and MURPHY, F. A. Wien Med. Presse, 1887
- 18 FOLGER, R. E. and MURPHY, F. A. Hyperthyroidism masked as heart disease, Boston Med. & Surg. Jr., 1924, cxx, 233-237
- 19 FOLGER, R. E. and MURPHY, F. A. Hyperthyroidism masked as primary heart disease, Med. Clin. N. A., 1925, 10, 1167-1171
- 20 FOLGER, R. E. and MURPHY, F. A. Hyperthyroidism masked as primary heart disease, Am. Jr. Med. Sci., 1923, 126, 1167-1171

THE CAUSE OF DEATH OF PATIENTS WITH ORGANIC HEART DISEASE SUBJECTED TO SURGICAL OPERATION*

By W K PURKS, M D , *Boston, Massachusetts*

AN EVALUATION of the ability of the patient with organic heart disease to withstand operation is a matter of great importance and also of great difficulty. In 1930, Butler, Feeney and Levine¹ wrote on the cardiac patient as a surgical risk. They reviewed 414 cases with organic heart disease who had been subjected to operation. Their study, contrary to some previous reports, indicated that these patients tolerate operation reasonably well. In their series, comprising 494 operations, there were 60 deaths, a mortality of 12.1 per cent. If those patients whose cardiac condition was such as to have produced death regardless of the operation, or whose surgical condition alone was sufficient to cause death, be excluded the mortality (unexpected mortality) was only 6.3 per cent. The present study consists of a detailed analysis of the causes of death in the 60 cases that were included in their report as compared with 60 non-cardiac patients who died following operation. It is hoped that such a study will throw some light upon the part played by an organically diseased heart in operative and postoperative mortality.

The patients comprising the 60 fatalities, as described in the original report, presented various types of heart disease including chronic valvular disease, chronic adhesive pericarditis, chronic myocarditis, angina pectoris, coronary thrombosis and thyroid heart disease. These cases are briefly summarized in table 1. The second group of non-cardiac cases was chosen from the surgical deaths of the Peter Bent Brigham Hospital regardless of the type of operation or anesthesia, the only essential criteria being that they had no history or physical signs of heart disease and, in the cases where an autopsy was done, showed negligible evidence of organic disease of the heart. An attempt was made to include the older patients in order that the ages in this group might be comparable to those in the cardiac group. Whereas the 60 deaths in the cardiac group resulted from 494 operations on 414 patients, the 60 deaths in the non-cardiac group represent the mortality (3.7 per cent) from approximately 1600 operations. In subsequent analysis it will be important to bear this difference in mind.

Early in the study it became obvious that it is not always easy, even in instances where an autopsy has been done, to state precisely the cause of death. After most careful study there remained in each group a number of cases where the cause of death had to be listed as unknown. This difficulty in deciding upon a single cause of death was more apparent in the

* Received for publication October 13, 1933

From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Massachusetts

TABLE I
Ordinary Patients
Death from Miscellaneous Causes

No.	Sex	Age	Disease	Operation	Anesthetic	Course
20	F	45	Emphysema	Amputation of leg	Gas oxygen	Temperature rise and bronchopneumonia at both bases. Death 9th day
21	M	35	Emphysema	Pharyngotomy	Novocaine	Continued septic course Death 8 hours p o Autopsy showed lobar pneumonia, empyema of pleura and mediastinum and pericarditis
22	F	44	Emphysema	Repair of hernia	Ether	Soon after operation increasing dyspnea, extrasystoles, rales at bases. Temperature rise to 101.2° F. Sudden change and death on 3rd day. Autopsy showed bronchopneumonia
23	F	35	Emphysema	Pharyngotomy	Gas oxygen	Rapid pulse and delirium, fever, decline and death in 3 months No positive blood cultures Cause of death endocarditis (? Gonococcus).
24	F	42	Emphysema	Pharyngotomy	Spinal novocaine	Continued fever reaching 101° F on 10th day Declining fever, increasing stupor Autopsy not done Cause of death unknown
25	M	45	Emphysema	Cholecystectomy	Ether	Anuria Pulse became irregular and weak Terminal temperature rise Death 2nd day Autopsy not done Cause of death unknown
26	F	31	Emphysema	Amputation of breast	Ether	Soon after operation became disoriented and incontinent Gradual decline Cheyne-Stokes respiration and uremia Cause of death. uremia
27	F	30	Emphysema	Amputation of leg	Gas-oxygen	Increasing stupor, rising temperature and dullness at lung bases Cause of death bronchopneumonia
28	F	41	Emphysema	Kraske 1 2	Ether	Nine days after second operation, temperature rise and edema of feet Infected wound On 14th day suddenly more dyspneic and died Cause of death (?) infection or congestive failure
29	M	38	Emphysema	Gastrojejunostomy	Gas-oxygen	On 8th day rise in temperature and signs of consolidation at bases Death 9th day Autopsy showed bronchopneumonia and empyema on the right
30	F	62	Emphysema	High amputation	Sacral and ether	At operation thrombus found in femoral vein, sudden death 2nd day Autopsy showed pulmonary embolus
31	M	60	Emphysema	Cholecystectomy	Ether	Third day fever and bronchial breathing at left base Increasing respirations, cyanosis and death Terminal temperature 102° F Cause of death bronchopneumonia
32	M	72	Emphysema	Repair of hernia	Novocaine	Second day marked dyspnea and cyanosis Increasing coma and death Cause of death unknown

Part A (Continued)

					Operation	Anesthetic	Course
14	M	Chronic myocarditis	Chronic myocarditis	Chronic myocarditis	Cholecystomy	Novocaine	Falling blood pressure, distention, decline and death 8th day. Autopsy showed carcinomatosis, bronchopneumonia
15	M	Chronic myocarditis	Chronic myocarditis	Chronic myocarditis	Cholecystomy Cholecystomy	Novocaine and ether	Decline and death 13th day. Autopsy showed bronchopneumonia
16	M	Chronic myocarditis	Chronic myocarditis	Chronic myocarditis	Cholecystomy	Novocaine	Decline and death 13th day. Autopsy showed bronchopneumonia
17	M	Chronic myocarditis	Chronic myocarditis	Chronic myocarditis	Cholecystomy	Ether	Sudden death on 16th day. Cause of death pulmonary embolus
18	M	Chronic myocarditis	Chronic myocarditis	Chronic myocarditis	Cholecystomy	Gas-oxygen ether	Continued state of shock, lapsed into coma and died on 3rd day. Cause of death cachexia and bronchopneumonia
19	M	Chronic myocarditis	Chronic myocarditis	Chronic myocarditis	Cholecystomy	Novocaine	Death on 8th day of peritonitis and partial obstruction.
20	M	Chronic myocarditis	Chronic myocarditis	Chronic myocarditis	Cholecystomy	Spinal, gas and ether	Death on 2nd day from liver necrosis due to accidental ligation hepatic artery
21	M	Chronic myocarditis	Chronic myocarditis	Chronic myocarditis	Cholecystomy	Gas-oxygen Novocaine	Eighteenth day after operation developed empyema. Later phlebitis
22	M	Chronic myocarditis	Chronic myocarditis	Chronic myocarditis	Cholecystomy	Novocaine	Long septic course and final death from pulmonary embolus
23	M	Chronic myocarditis	Chronic myocarditis	Chronic myocarditis	Cholecystomy	Ether	Second day death with lobar consolidation at both bases. Confirmed by autopsy
24	M	Chronic myocarditis	Chronic myocarditis	Chronic myocarditis	Cholecystomy	Gas-oxygen	Sudden death apparently from pulmonary embolism
25	M	Chronic myocarditis	Chronic myocarditis	Chronic myocarditis	Cholecystomy	Novocaine	Spreading infection in foot and leg. Death from bronchopneumonia 19th day
26	F	Chronic myocarditis	Chronic myocarditis	Chronic myocarditis	Cholecystomy	Novocaine	Sudden death 4 hours after operation, interpreted as pulmonary embolism

Part A (Continued)

Age	Sex	Surgical Diagnosis	Cardiac Diagnosis	Operation	Anesthetic	Course
58	M	Carcinoma stomach	Endocarditis (acute)	Laparotomy	Ether	Up in chair 29th day Slight fever Pulmonary infarcts Hemiplegia, decline and death 47th day Autopsy thromboses (inferior vena cava, pulmonary arteries, coronary), acute endocarditis and carcinoma
66	F	Carcinoma sigmoid	Chronic myocarditis	Sigmoidostomy	Novocaine	Incarcerated diaphragmatic hernia not relieved at operation Decline and death 12 hours after operation Autopsy cause of death, intestinal obstruction
67	M	Prolapse rectum	Chronic myocarditis	Whitehead (modified)	Novocaine	Increasing stupor, rising B U N Death from uremia (autopsy)
49	F	Carbuncles	Chronic myocarditis	Incision and drainage	Gas-oxygen	Continued stupor, decline and death Cause of death unknown
65	M	Carcinoma penis	Chronic myocarditis	Resection of glands	Novocaine	Bronchopneumonia 9th day Decline and death Autopsy showed thrombosed iliac veins, bilateral pulmonary emboli with congestion and edema Cause of death pulmonary embolism
64	F	Carcinoma esophagus	Chronic myocarditis	Gastrostomy	Novocaine	Decline and death on 23rd day Autopsy showed mediastinal abscess and bronchopneumonia
65	M	Carcinoma bladder	Coronary sclerosis	Excision of tumor	Spinal	Sudden death 27th day Autopsy showed pulmonary embolus

Part B (Death from Congestive Heart Failure)

Age	Sex	Surgical Diagnosis	Cardiac Diagnosis	Operation	Anesthetic	Course
37	F	Valvular D Ad pericard	Same	Cardiolysis	Ether	Immediately after operation began to fill with edema and died in 8 hours Autopsy mitral stenosis, tricuspid stenosis, old infarcts in lungs, etc
43	M	Adhesive pericarditis	Same	Cardiolysis	Ether	Operation lasted 4 hours Lungs soon filled with fluid, increasing dyspnea and death on 3rd day Autopsy limited to heart
72	M	Prostatism	Chronic myocarditis	Prostatectomy	Spinal	On 2nd day developed auricular fibrillation, increasing dyspnea and died Autopsy showed interlobar effusion, slight bronchopneumonia
35	F	Mitral stenosis	Same	Cardiotomy	Ether	Long operation Heart stopped once during procedure P O increasing dyspnea and death within 24 hours Autopsy limited to the heart
63	M	Cholelithiasis	Chronic myocarditis	Valvulotomy Cholecystectomy	Ether	Second day developed moist râles at bases Digitalized without effect and died 2nd day Autopsy showed hydrothorax, pulmonary congestion and early bronchopneumonia

Part C. (Death Due to Coronary Occlusion)

	Age	Pre-morbid	Operation	Anesthetic	Course
24	57	Coronary infarct	Pericardiectomy	Spinal	Wound infection Attempted secondary closure 27th day 29th day suddenly dyspneic, cyanotic, died in 30 minutes Autopsy large softening in heart, mural thrombi, congestion
28	51	Coronary occlusion	Hemithoracotomy	Novocaine	Developed emphysema during treatment for coronary occlusion Seventh day after operation suddenly more dyspneic, cyanotic and died
30	50	Chronic myocarditis	Hysterectomy	Ether	First carried to operating room, had a fall in blood pressure and operation was delayed 2 days Immediately after operation again had fall in blood pressure, 9th day suddenly became weak and died
31	48	Stenosis of heart	Repair	Ether	Sudden death 6 hours after operation Autopsy showed occlusion of right coronary
34	47	Coronary infarct	Excision and prostatic-tomy	Gas oxygen	Sudden death on 3rd day Autopsy showed cardiac infarct with rupture
36	46	Angina pectoris	Leg amputation	Novocaine and spinal	Coronary occlusion 1 week previously Hurried amputation Decline and death 2nd day Autopsy showed extensive cardiac infarct and many small pulmonary emboli
42	41	Coronary occlusion	Popliteal ligation	Novocaine	Ten days after amputation was apparently doing well when he suddenly became dyspneic and died Autopsy showed thrombosis left coronary, mural thrombi in aorta and femoral artery
43	41	Coronary infarct	Amputation Hemorrhoidectomy	Gas oxygen Gas-oxygen	Operation immediately followed by dyspnea and cyanosis Electrocardiogram showed coronary changes Flaccid paralysis on left, rapid decline and death on 4th day Autopsy showed large cardiac infarct Also cerebral infarct

Part D (Death Due to Cerebral Accidents)

	Age	Pre-morbid	Operation	Anesthetic	Course
44	41	Chronic myocarditis	Amputation of toe	Gas oxygen	Uneventful course until 7th day when suddenly became unconscious, developed hemiplegia, tracheal râles, and died
45	41	Mural stenosis	Ligation brachial	Ether	Satisfactory course until 4th day, suddenly unconscious, developed hemiplegia, progressive decline and death on 22nd day

cardiac group This difference is probably, in a measure at least, due to a greater occurrence in the cardiac group of such more or less intangible factors as peripheral vascular collapse In such instances one cannot attribute the cause of death to the heart per se though the damaged heart may contribute to the causation or continuation of such a state of vascular collapse This state of impaired circulation probably also predisposes to uremia in instances where the kidney function has previously been impaired and also predisposes to thromboses in the visceral, cardiac, and cerebral vessels if these structures are the site of any preëxisting disease

TABLE II

	Cardiacs	Non-Cardiacs
Number of patients	414	1600
Number of deaths	60	60
Autopsies	38	43
Average age	58.9 years	51.5 years
Males	30	39
Females	30	21

TABLE III

Causes of Death

	Cardiacs		Non-Cardiacs	
	Chief	Contributing	Chief	Contributing
Unknown	9		6	
Congestive heart failure	5	9	0	0
Coronary occlusion	8	1	0	0
Cerebral accident	2	3	0	0
Pulmonary embolus	7	2	10	1
Infection	17	16	29	8
Infarction	0	7	1	2
Uremia	5	0	2	1
Hemorrhage	1	0	3	0
Cachexia	1	3	4	7
Thyroid storm	3	0	0	0
Liver necrosis	1	0	0	0
Intestinal obstruction	1	0	0	0
Purpura	0	0	1	0
Air embolus	0	0	1	0
Anesthetic	0	0	2	0
Hyperinsulinism	0	0	1	0

Comparative data on the two groups are presented in tables 2 and 3 In the group of cardiac patients there were 30 males and 30 females with an average age of 58.9 years Thirty-eight of these were studied post mortem In the group of non-cardiac patients there were 39 males and 21 females with an average age of 51.5 years Forty-three autopsies were performed in this group The younger age in the latter group is undoubtedly due to the fact that many patients past 50 years of age had either clinical or pathologic evidence of some degree of heart disease and therefore had to be excluded Analysis of the causes of death shows several things of note In the cardiac group there are causes such as congestive heart failure, coronary occlusion and cerebral accidents which do not exist in the non-cardiac as principal or contributing causes, the difference being

largely made up by the greater incidence of infection in the latter group. There is also a much greater incidence of contributing causes in the cardiac group. Contrary to what one might have expected, infarction other than that resulting from coronary occlusion, though frequently a contributing cause, was not chiefly responsible for death in any patient of group one. Pulmonary embolism appears more frequently as a cause of death in the non-cardiac group. This does not by any means indicate that pulmonary embolism occurs more frequently in the non-cardiac patient. Indeed it must be apparent that if pulmonary embolism occurred seven times as a cause of death in 414 patients and only 10 times as a cause of death in 1600 non-cardiac patients, the true incidence is considerably higher in the former group. By a similar analysis the incidence of fatal hemorrhage in the two types of cases appears to be about the same. In this study the unusual causes of death do not occur with sufficient frequency to warrant comparison of the two groups. The greater incidence of uremia in the cardiac patients is to be expected because of the association of renal and cardiac disease.

Let us now consider those causes such as congestive heart failure, coronary occlusion, and cerebral accidents which do not exist in the non-cardiac cases (see table 1, parts B, C, and D). Such causes accounted for one-fourth of the deaths in the cardiac patients. Of the five instances of congestive heart failure as a cause of death three were patients who had operations on the heart itself (cardiomyolysis or valvulotomy) and may therefore be disregarded insofar as general operative mortality is concerned. There remain then only two cases where congestive failure was the major factor in causing death. In view of the fact that a large number of the patients comprising the original series of 414 patients had evidence of congestive failure at some time during the period of observation this low percentage appears definitely to indicate that congestive heart failure is not a major hazard in operations upon the well treated cardiac. Its effect as a contributing cause of death is difficult to assess. Along with infarction it was probably a factor in causing the relatively greater incidence of fatal pulmonary infection in the cardiac group. Often in the cases where pulmonary infection was decided upon as the cause of death there was also clinical or pathologic evidence of pulmonary congestion or infarction. Wherever it seemed probable that in the absence of infection the individual might have survived the effects of the other pulmonary pathology the cause of death has been attributed to the infection. When we come to consider the cases where coronary occlusion was the cause of death it is clear that, though some of this group of eight patients would undoubtedly have died even if the operation had not been done, there were a number who might otherwise have survived. Cerebral accident appears to have been the cause of death in only two instances though its incidence as a contributing factor is slightly greater. It is probably true that in the cardiac the liability to cerebral accidents is somewhat increased by operation.

What causes, then, account for the increased hazard of operations upon the cardiac patient as compared with the non-cardiac patient? The present study indicates that congestive heart failure is not a significant factor in increasing the mortality of the cardiac except as it may contribute to a predisposition to pulmonary infection. The cardiac patient in a ratio of about four to one seems more liable to fatal pulmonary infection than does the non-cardiac. The greater incidence of fatal pulmonary embolism and the effect of coronary occlusion or its sequelae are likewise major factors in increasing the risk of operation upon the cardiac patient.

SUMMARY

(1) The causes of death of 60 patients with organic heart disease who have been subjected to operation are compared with the causes of death in a similar group of 60 non-cardiac patients.

(2) This study indicates that in the well treated cardiac, congestive

heart failure is not a very significant factor in the causation of death following operation

(3) The cardiac group differs from the non-cardiac chiefly in the presence of fatal coronary occlusion and in the greater incidence of fatal pulmonary complications, chiefly infection and pulmonary embolism

I wish to express my appreciation to Dr Samuel A Levine for his assistance in this study

REFERENCE

- 1 BUTLER, S, FIFNEY, N, and LEVINE, S A The patient with heart disease as a surgical risk, review of 414 cases, Jr Am Med Assoc, 1930, xcvi, 85-91

MYELOID INSUFFICIENCY *

By R. GOTTLIEB, M Sc, M D, *Montreal, Canada*

THERE is a group of anemias with a blood picture of an exhausted myeloid system, showing little or no signs of regeneration. The blood picture is that of an anemia, granulocytopenia, and thrombocytopenia. In some of these cases the etiology is known, e.g., arsenic or benzol poisoning, in others the etiological factor cannot be found. In the literature these cases are referred to as "aplastic anemia," "myelophthisic anemia," "aleukia hemorrhagica," etc., but none of these terms properly expresses the character of the condition. We are really dealing with an insufficiency of the myeloid system. A myeloid insufficiency may involve the entire system or only parts of it. In the so-called "malignant neutropenia" or "agranulocytosis" only the granulopoietic apparatus is involved. The close pathogenic relationship of these cases of agranulocytosis and aplastic anemia is expressed in the fact that a number of the agranulocytoses eventually develop the picture of a complete myeloid insufficiency with anemia and thrombocytopenia.¹ The same is true of arsenic and of benzol poisoning in which either part or the whole myeloid system may be involved. The question now arises as to the way in which a poison or toxin affects the myeloid system. Is it a direct action on the myeloid system, or does the toxin or poison act through a disturbance of the normal balance in the hematopoietic system? It is a well known fact that the normal myeloid system per se has a tendency to extensive proliferation, this proliferation is kept in check by the reticulo-endothelial system. A removal of the normal inhibition leads to an extensive proliferation of the myeloid system, as can be seen experimentally in animals after the removal of the spleen, or in the human after a normal spleen has been removed for some mechanical reason (e.g., traumatic ruptured spleen). The myeloid proliferation lasts as long as it takes for the reticulo-endothelial system to make up for its loss by proliferation in other places (Kupffer cells, accessory spleens, etc.). We know that the normal reticulo-endothelial system has an inhibitory effect on the normal myeloid system. In infections in which a reticulo-endothelial proliferation is met with, the myeloid system is usually depressed. Such is the case for instance in typhoid fever, influenza, miliary tuberculosis and in other conditions in which leukopenia, anemia, and purpura are so frequently present. Although a direct action of an infectious agent, a poison or a toxin, on the myeloid system cannot entirely be denied, or at least not at certain stages, the importance of a disturbed equilibrium of hematopoiesis must be borne in mind, especially the possibility that a stimulated and pro-

* Read before the Annual Clinical Session of the American College of Physicians, February 10, 1933.

From the Department of Medicine, McGill University Clinic, Royal Victoria Hospital, Montreal.

This research was made possible by a grant from the Banting Research Foundation.

hyperplastic reticulo-endothelial system may increase its physiological inhibition to a pathological degree. If such a pathological inhibition persists even after the original cause has been removed, it is only logical that a complete atrophy of the myeloid system may result.

The case presented here is an example of a complete myeloid insufficiency of unknown etiology.

CASE REPORT

A male patient, age 19, first came under observation on August 1, 1932. His only complaints were progressive weakness, pallor, and bleeding from the gums. His past history was of no importance. He was a high-school student and very active in athletics. About one year previously, the patient had noticed he would tire more quickly when playing tennis or other games but, being otherwise well, he ignored this. In April 1932 the patient had a cold which lasted for about two weeks, at this time he first noticed bleeding from his gums. Since that time he became progressively weaker and paler, and bleeding from the gums became quite profuse during July. On July 20, he received a transfusion, with improvement for a few days.

On August 1, 1932, examination revealed the following facts: temperature normal, pulse 96, respiration 20, good nutrition, marked pallor with a slightly greenish tinge, bleeding from the gums, positive Frank-Hess sign, spleen just palpable. The physical examination did not otherwise reveal anything abnormal. Urine, stool, and gastric analyses were normal.

Hematological examination: Red blood cells 1,270,000; hemoglobin 32 per cent (4.48 gm/100 cc. of blood), color index 1.3, white blood cells 2,550, thrombocytes 68,000, reticulocytes 2 per cent. The differential count showed a marked granulocytopenia and 69 per cent lymphocytes. Bleeding time was prolonged, coagulation time normal, clot retraction absent.

In spite of the normal gastric acidity 20 cc. of liver extract (FD) were injected intravenously on the same day without any appreciable effect for the next 10 days.

The patient was admitted to the hospital on August 5, his condition having become worse. Examination showed: Red blood cells 1,120,000; hemoglobin 25 per cent; color index 1.13; white blood cells 2,150; thrombocytes 10,000. Profuse bleeding from the gums was present. The adrenalin test showed a fair myeloid response in 20 minutes, leading to an increase of the white blood cells from 1,900 to 7,800, with a return to the original level within one hour. (See chart 1.)

The clinical picture, together with the hematological examination, suggested an exhausted myeloid system, leading to a reduction of all myeloid elements, that is, anemia, granulocytopenia, and thrombocytopenia; signs of regeneration, although not entirely absent, were slight.

Based on the assumption of the reticulo-endothelial inhibition being the cause of the myeloid insufficiency it was decided to remove the spleen in order to relieve the myeloid system of part of that inhibition. The absence of an infection and the fair myeloid response in the adrenalin test were further aids in the decision.

Two transfusions were given to the patient prior to the operation, and the spleen was removed on August 10. The spleen was slightly larger than normal. Sections showed a thin overlying capsule, normal appearing trabeculae, well formed vascular channels free from hyaline changes and surrounded by a comparatively large amount of lymphoid tissue for this age period. The pulp was cellular, containing in addition to numerous lymphocytes occasional polymorphonuclear and eosinophile leukocytes. The reticular cells were hyperplastic and appeared as large phagocytic elements. The venous sinuses were not conspicuous and appeared rather compressed by the pulp and were lined by rather swollen looking reticulo-endothelium which projected into

TABLE I
Detail blood findings

Date—1932.....	August 1,	August 5	August 6	August 7	August 8
Hb.....	32% 4.48 gm.	25% 3.25 gm.	35% 4.90 gm.	45% 6.30 gm.	45% 6.30 gm.
R.B.C.....	1,270,000	1,120,000	1,630,000	1,800,000	1,700,000
C.I.....	1.33	1.13	1.09	1.25	1.32
Reticulocytes.....	2%	2½%	2½%	2%	2%
Nucleated R.B.C.....	0	0	0	0	0
W.B.C.....	2550	2150	1800	1900	2000
Basophiles.....	0	0	0	0	0
Eosinophiles.....	3%	2%	2%	3%	3%
Myeloblasts.....	75	42	36	57	60
Myelocytes.....	0	0	0	0	0
Meta. myelocytes.....	0	0	0	0	0
Stab. forms.....	1%	2%	3%	4%	4%
Polysegmented.....	25	42	54	76	80
Lymphocytes.....	25%	24%	25%	23%	25%
Monocytes.....	625	504	450	247	500
Thrombocytes.....	69%	69%	68%	67%	65%
Remarks.....	1725	1449	1224	1273	1300
	2%	3%	2%	3%	3%
	50	63	36	57	60
	68,000	10,000	45,000	40,000	40,000
	6 days after transfusion	Admission	24 hrs. after transfusion		

TABLE I (continued)

Date.....	August 9	August 10 9 a.m.	August 10 ½ hour P.O.	August 10 4 hours P.O.	August 11
Hb.....	41%	46%	44%	44%	42%
R.B.C.....	5.74 gm.	6.44 gm.	6.16 gm.	6.16 gm.	5.88 gm.
C.I.....	1,900,000	2,100,000	2,100,000	2,000,000	2,000,000
Reticulocytes.....	1.07	1.09	1.04	1.1	1.05
Nucleated R.B.C.....	2%	2%	2%	2%	2½%
W.B.C.....	0	0	0	0	0
Basophiles.....	2200	1900	3100	3100	3000
Eosinophiles.....	0	0	0	0	0
Myeloblasts.....	0	0	0	0	0
Myelocytes.....	2%	2%	2%	2%	2%
Meta. myelocytes.....	44	38	0	0	0
Stab. forms.....	0	0	0	0	0
Polysegmented.....	0	0	0	0	0
Lymphocytes.....	0	0	2%	3%	5%
Monocytes.....	0	0	62	93	150
Thrombocytes.....	0	0	3%	5%	7%
Remarks.....	0	0	93	155	210
	3%	3%	5%	22%	15%
	66	57	155	682	450
	26%	23%	22%	20%	17%
	575	247	682	620	510
	67%	70%	64%	45%	52%
	1474	1330	1984	1395	1560
	2%	2%	4%	5%	3%
	44	38	124	155	90
	30,000	55,000	150,000	250,000	175,000
	Transfusion	Splenectomy	½ hour P.O.	4 hours P.O.	
	500 c.c.				

TABLE I (continued)

Date.....	August 12	August 13	August 15	August 16	August 17
Hb.....	45%	45%	48%	50%	48%
R.B.C.....	6.30 gm.	6.30 gm.	6.72 gm.	7.00 gm.	6.72 gm.
C.I.....	2,200,000	2,310,000	2,420,000	2,575,000	2,630,000
Reticulocytes.....	1.02	0.97	1	1	0.92
Nucleated R.B.C.....	4½%	5%	5½%	6%	5%
W.B.C.....	+	+	+	+	+
Basophiles.....	3100	3300	3600	3900	3950
Eosinophiles.....	0	0	0	0	1%
Myeloblasts.....	0	0	0	0	3%
Myelocytes.....	0	0	1%	2%	2%
Meta. myelocytes.....	0	0	36	78	78
Stab. forms.....	0	0	2%	1%	0
Polysegmented.....	62	66	72	39	0
Lymphocytes.....	5%	4%	5%	4%	3%
Monocytes.....	152	132	180	156	117
Thrombocytes.....	9%	6%	5%	5%	4%
Remarks.....	279	195	180	195	156
	16%	12%	11%	10%	10%
	49%	39%	39%	39%	39%
	13%	20%	20%	22%	24%
	403	620	720	855	936
	51%	52%	52%	53%	51%
	1581	1716	1972	2097	2109
	4%	4%	4%	3%	3%
	124	132	141	117	117
	125,000	106,000	125,000	137,000	122,000

TABLE I (continued)

Date	August 19	August 22	August 24	August 26	August 29	Septem- ber 1
Hb.....	45% 6.30 gm. 2,450,000	46% 6.44 gm. 2,540,000	45% 6.30 gm. 2,400,000	40% 5.60 gm. 2,200,000	42% 5.88 gm. 2,250,000	44% 6.16 gm. 2,400,000
C.I.....	0.93	0.92	0.93	0.90	0.95	0.91
Reticulocytes.....	5%	5%	8%	7.5%	7%	5.5%
Nucleated R.B.C.....	0	0	0	0	0	0
W.B.C.....	4100	4200	4600	4900	5900	5800
Basophiles.....	0	0	0	0	0	0
Eosinophiles.....	2%	2%	2%	2%	2%	2%
Myeloblasts.....	82 2%	84 1%	92 0	98 1%	118 0	116 0
Myelocytes.....	82 4%	42 2%	0 3%	49 2%	0 2%	0 1%
Meta. myelocytes.....	164 4%	84 2%	138 2%	98 3%	118 4%	58 5%
Stab. forms.....	164 10%	84 10%	92 8%	147 10%	236 12%	290 12%
Polysegmented.....	410 25%	420 34%	368 36%	490 38%	708 36%	696 37%
Lymphocytes.....	1025 50%	1428 47%	1656 47%	1862 41%	2124 41%	2146 40%
Monocytes.....	2050 3%	1974 2%	2162 2%	2009 3%	2419 3%	2320 3%
Thrombocytes.....	123 133,000	84 142,000	92 122,000	147 100,000	117 150,000	174 148,000
Remarks.....						

TABLE I (continued)

Date.....	September 10	September 19	September 26	October 1	October 6
Hb.....	70% 9.80 gm. 3,600,000	82% 11.48 gm. 4,300,000	48% 6.72 gm. 2,700,000	60% 8.40 gm. 3,180,000	60% 8.40 gm. 3,220,000
C.I.....	0.97	0.95	0.88	0.96	0.93
Reticulocytes.....	4%	4%	12%	6%	2%
Nucleated R.B.C.....	0	0	++	+	0
W.B.C.....	6300	6400	7200	6200	7100
Basophiles.....	0	0	0	0	0
Eosinophiles.....	0	0	0	0	0
Myeloblasts.....	2%	2%	2%	3%	3%
Myelocytes.....	126 0	128 0	144 0	186 0	213 0
Meta. myelocytes.....	0 0	0 0	3% 216	0 0	0 0
Stab. forms.....	0 2%	0 2%	6% 432	3% 186	3% 213
Polysegmented.....	126 8%	128 6%	15% 1080	10% 620	11% 781
Lymphocytes.....	504 44%	374 45%	30% 2160	40% 2480	39% 2769
Monocytes.....	2772 39%	2880 40%	38% 2736	40% 2480	40% 2840
Thrombocytes.....	2457 5%	2560 4%	6% 432	4% 248	4% 284
Remarks.....	305 162,000	256 146,000	79,000 Cold. Trans- fusion 500 c.c.	153,000	170,000

TABLE I (continued)

Date.....	October 10	October 15	October 18	October 20	October 24
Hb.....	50%	35%	35%	18%	10%
	7.00 gm.	4.90 gm.	4.90 gm.	2.52 gm.	1.40 gm.
R.B.C.....	2,700,000	1,900,000	1,800,000	910,000	560,000
C.I.....	0.92	0.92	0.97	1	1
Reticulocytes.....	0.5%	0.5%	0	0	0
Nucleated R.B.C.....	0	0	0	0	0
W.B.C.....	6800	10,000	12,000	11,000	12,000
Basophiles.....	0	0	0	0	0
	0	0	0	0	0
Eosinophiles.....	2%	2%	1%	1%	0
	136	200	120	110	0
Myeloblasts.....	0	0	0	0	1%
	0	0	0	0	120
Myelocytes.....	0	2%	3%	2%	4%
	0	200	360	220	480
Meta. myelocytes.....	4%	6%	6%	7%	8%
	272	600	720	770	960
Stab. forms.....	12%	14%	12%	13%	15%
	816	1400	1440	1430	1800
Polysegmented.....	40%	38%	40%	38%	34%
	2720	3800	4800	4180	4080
Lymphocytes.....	37%	32%	33%	34%	32%
	2516	3200	3960	3740	3840
Monocytes.....	5%	6%	5%	5%	6%
	340	600	600	550	720
Thrombocytes.....	120,000	60,000	50,000	20,000	1000
Remarks.....		Transfusion 500 c.c.	Profuse bleeding	Broncho- pneumonia	

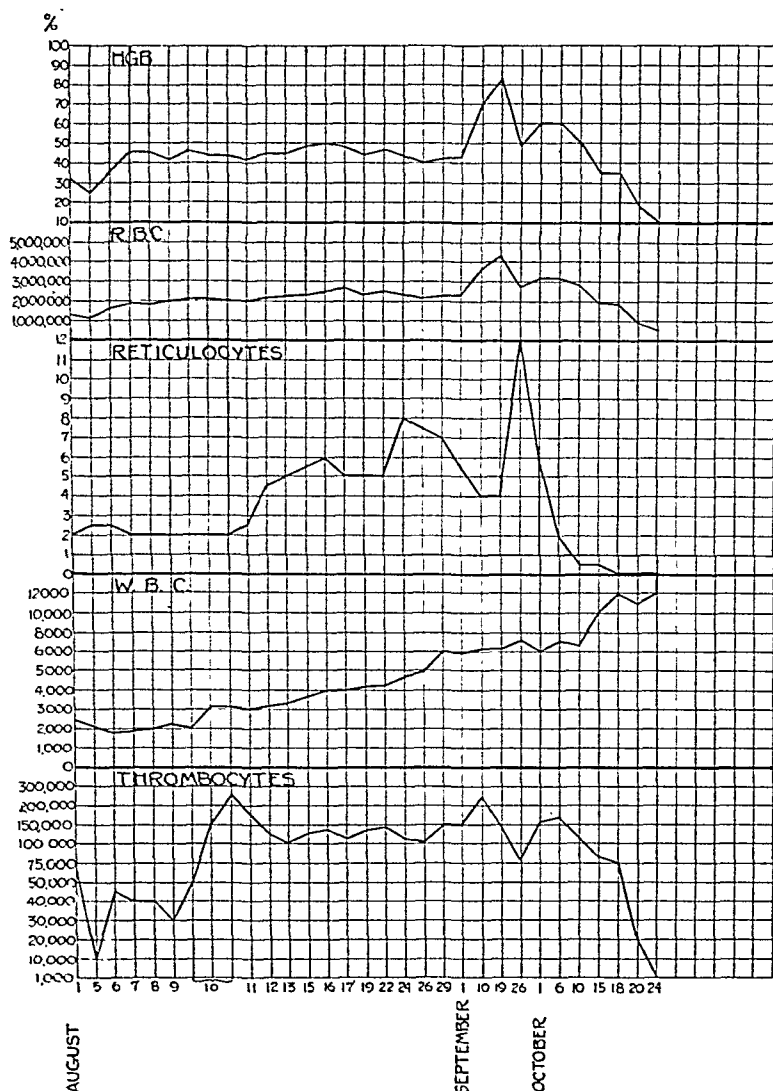
the films. Special stains showed the following: (1) There was a moderate number of blue staining cells by the oxydase reaction. These were for the most part found in the cellular exudate in the pulp but there appeared to be occasional small foci of myeloid metaplasia. (2) Stain for reticulin: This was found well preserved as a finely meshed interlacing network. (3) Special stain for collagen fibrils showed no appreciable increase.

Following the splenectomy there was an almost instantaneous improvement. The blood picture quickly assumed a hyperregenerative character (details may be seen in table I and chart 2). Figure 1, which is composed from six different fields, shows the different young forms, and the rapidly forming platelets which were often found to be still in protoplasmic connection. The wound healed normally; the patient improved steadily, and was discharged from the hospital on September 2, 1932. From September 2 to September 20 the patient was perfectly well. On September 20 he developed a cold and started to go rapidly downhill. A transfusion was given on September 26 which led to a short temporary improvement. The anemia became progressively worse, however, and a transfusion was again given on October 10 with little success. On October 20 the patient developed bronchopneumonia and died on October 26. An autopsy could not be obtained.

Although the result of the splenectomy showed only a temporary improvement, we feel inclined to believe that our method of procedure was justified. Since patients with acute idiopathic myeloid insufficiency are doomed to die in a short time, any attempt to save them, or at least prolong their life, is justified. We may perhaps add that early operation is essential and should be guided in the indication by the finding of a bone-marrow hi-

opsy (which unfortunately was not done in this case), since one can hardly expect a regeneration to occur from a completely fatty myeloid system. Other points of importance which one must consider are the results of the adrenalin test, and the absence of infection.

CHART 2. Blood findings



SUMMARY

1. A case of idiopathic (essential) myeloid insufficiency is reported.
2. A possible explanation for the pathogenesis is offered.
3. Early splenectomy is suggested as a possible means to combat the disease.

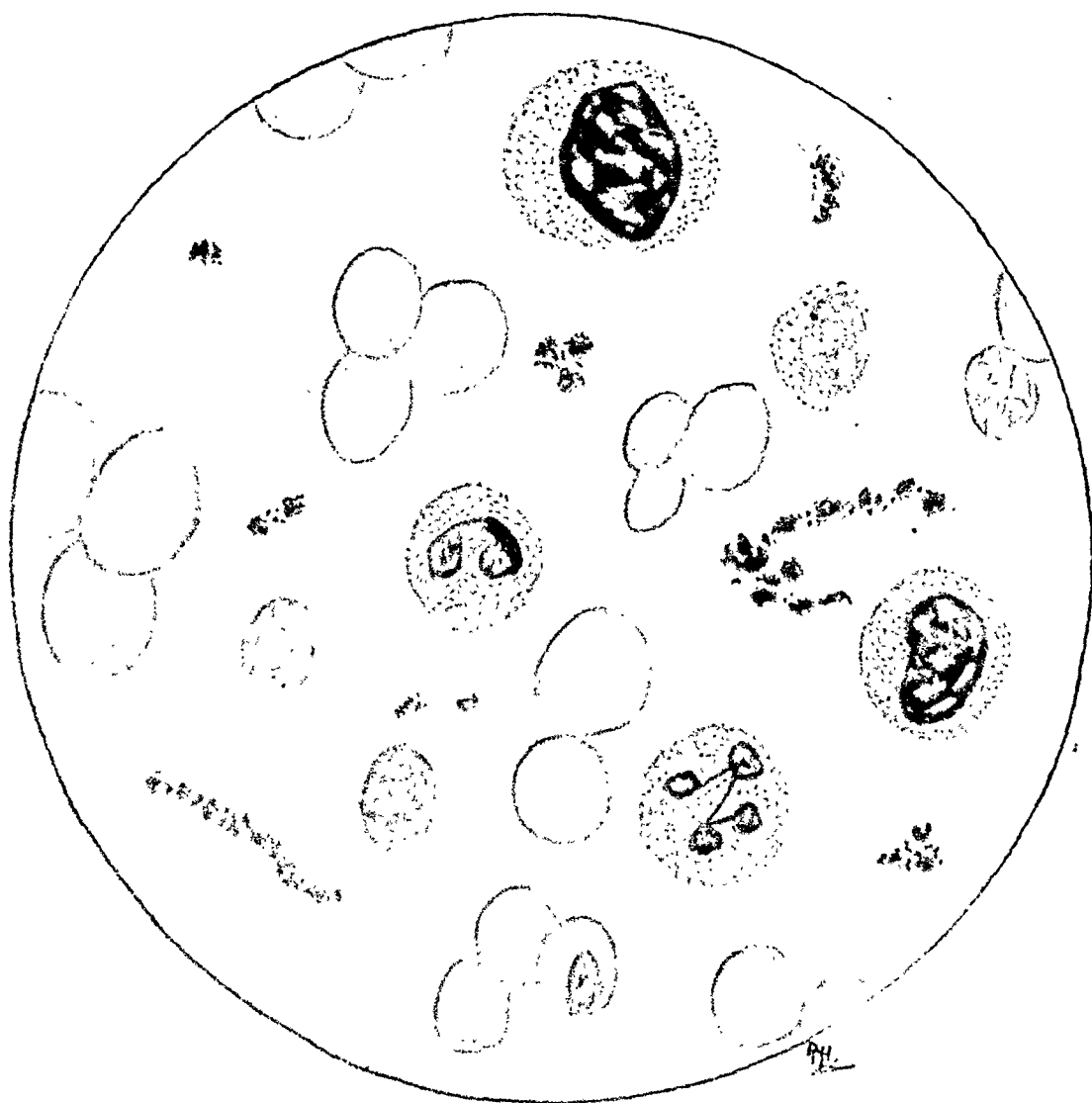


FIG. 1. Blood picture after splenectomy.

BIBLIOGRAPHY

1. Luzzati, P.: Die Hämorrhagischen Diathesen, *Enzyklopädie d. klin. Med. Die Krankheiten d. Blutes u. der blutbildenden Organe*, 1925, ii, Springer, Berlin, p. 289.
2. Rosenbaum, N.: Hematological aspect of agranulocytosis and other diseases accompanied by neutrophilopenia, *Am. Jr. Clin. Path.*, 1931, i, 7-22.

THE IMPORTANCE OF BRONCHOSCOPY IN BRONCHIECTASIS *

By HORACE P. MARVIN, M.D.,† *Honolulu, Hawaii*

BRONCHOSCOPY plays a very important part in both the diagnosis and treatment of cases of bronchiectasis. Practically all of the limited literature on this subject has been contributed by the bronchoscopist or the surgeon, with an occasional brief note by an internist. Jackson states that "in most cases of bronchiectasis there are strong indications for a bronchoscopic diagnosis." Ballon, Singer and Graham report that "the bronchoscope is a great aid in the diagnosis of bronchiectasis," and also state that "the value of the bronchoscope in the treatment of foreign body bronchiectasis and in certain cases which are due to partial bronchial stenosis is obvious."

It is not the purpose of this paper to attempt any discussion of bronchoscopic technic, but to present the writer's conclusions on the present subject strictly from the standpoint of the internist. These conclusions have been reached after treating 117 cases of bronchiectasis in the past three years, as well as reviewing the clinical records of 83 additional cases which had been treated in this hospital prior to July 1930, making a total of 200 cases. Seventy per cent, or 147, of these 200 cases had diagnostic bronchoscopies, whereas 44 per cent, or 89 patients, had therapeutic bronchoscopies which varied in number from 1 to 63. Ninety per cent of the cases treated in the past three years have been bronchoscoped for diagnostic purposes and approximately 50 per cent received bronchoscopic treatments.

There is no doubt as to the additional diagnostic data which may be obtained from careful bronchoscopy, especially when there is close co-operation between the bronchoscopist and the internist. A careful examination and detailed report by the bronchoscopist may be the deciding factors in determining the exact etiology, the location of the lesions and the diagnosis in a given case. As mentioned above, bronchiectasis caused by foreign bodies or bronchial strictures are readily detected by bronchoscopic examination and the foreign body can usually be removed or the stricture dilated, thus eliminating the cause and making the prognosis much better. Of much importance to the internist is a report which includes the color and condition of the mucous membrane of the bronchi as well as the nature, amount and location of the secretion when present. In the early or milder cases the bronchoscopist usually reports the mucous membrane as grayish and glazed in appearance, with varying amounts of muco-purulent or purulent sputum in the bronchi affected. In the more advanced cases, the mucous membrane is often reported as thickened, leathery or edematous in

* Received for publication March 31, 1933.

From the Bronchiectasis Branch of the Medical Service, Fitzsimons General Hospital. Published by permission of The Surgeon General, U. S. Army.

† Captain, Medical Corps, U. S. Army.

appearance with from 20 c.c. to 60 c.c. of purulent secretion aspirated from the involved areas of bronchiectasis. It is our custom to obtain a specimen and culture of the uncontaminated secretion, which is aspirated and sent to the laboratory in a sterile test tube. A number of different organisms have been cultured from the deep sputum thus obtained, but the organisms usually reported by the laboratory as predominant have been a non-hemolytic streptococcus, the *Staphylococcus albus*, Friedländer's bacillus, and the micrococcus catarrhalis. Sometimes the bronchoscopist reports that he can see the dilatations in the terminal bronchi. Not infrequently the retained secretion in the dilated bronchi is so thick and crusted as to require softening by injecting some warm fluid before complete aspiration can be accomplished. This is a very important procedure in such cases prior to injecting lipiodol for bronchography, otherwise the retained crusted secretion will not allow the lipiodol to fill the bronchiectatic cavities, which results in a negative bronchogram.

In addition to the above mentioned diagnostic information gained by bronchoscopy, this procedure allows the operator to inject the lipiodol by means of the bronchoscope. By so doing, the operator knows that the lipiodol is being instilled into the bronchi rather than entering the esophagus. This latter sometimes happens, especially with an unintelligent or uncooperative patient when the lipiodol is instilled without the scope, even when the best technic is used by the operator. We have obtained several excellent bronchograms by using what we term the "instillation method" (without bronchoscopy), but in many cases in 1930 and 1931, we found it necessary to do a bronchoscopic aspiration and injection of lipiodol after attempting the "instillation method" first. Although the patient may attempt complete emptying of his bronchiectatic cavities by careful postural drainage, yet this may not be possible or may be unsatisfactory due to factors already mentioned. At the present time we request a diagnostic bronchoscopy and instillation of lipiodol for bronchograms in all cases. The information gained from the bronchoscopy plus the bronchogram has usually resulted in arriving at an early and satisfactory conclusion as to the exact nature of the pathologic lesions present. These data furnish additional evidence to support the impressions gained from the history, physical examination and the type of sputum noted following postural drainage. In other words, diagnostic bronchoscopy and bronchography either establish the diagnosis early and conclusively or are of material aid in substantiating the diagnosis of bronchiectasis made clinically at the time the patient was admitted to the hospital.

As important as bronchoscopy has proved to be as an aid in the diagnosis of bronchiectasis, yet it is of much more importance from a therapeutic standpoint. It is a generally accepted fact that the treatment of this disease may be summed up in the two words "bronchial drainage." These two words do not cover all types of therapy, but they do express the main objective in the treatment of bronchiectasis. Bronchial drainage may be

obtained in three ways: (a) postural drainage; (b) bronchoscopic drainage; (c) surgical drainage.¹ Postural drainage is by far the most important of the three methods. This should be practiced consistently and energetically and may be accomplished in any one or more of several ways.

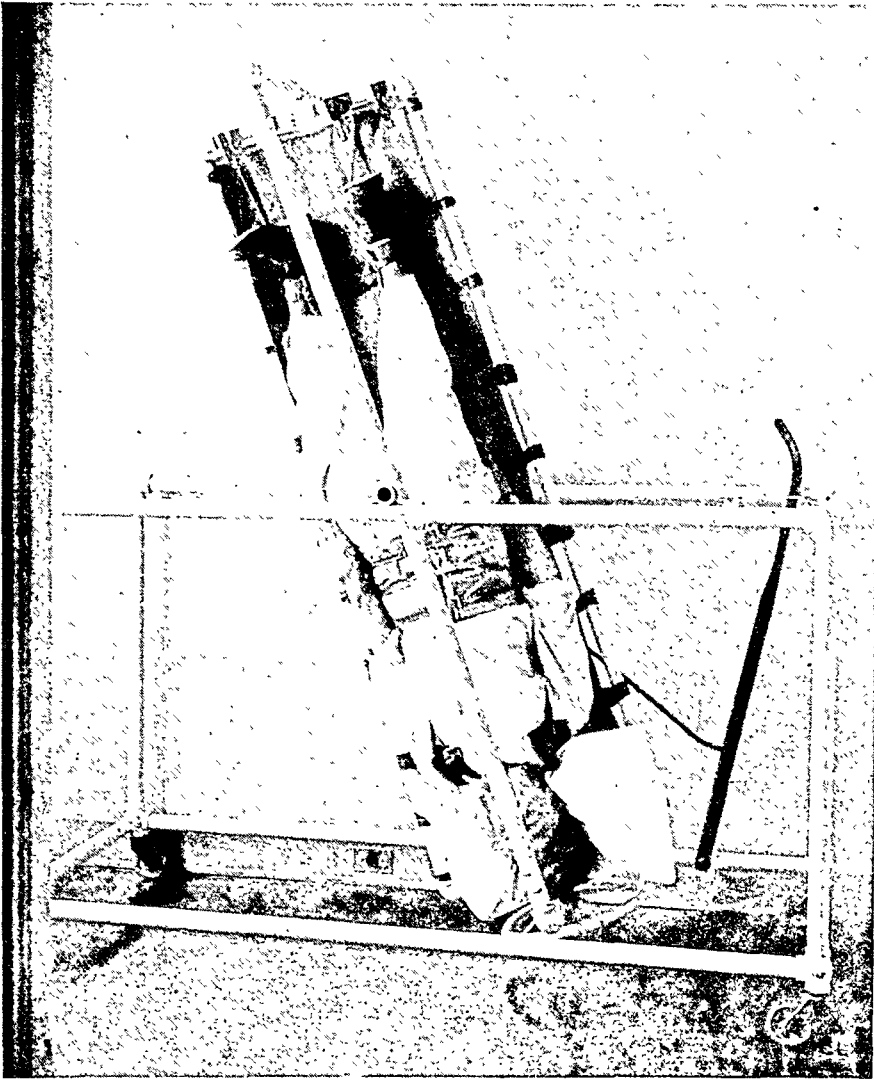


FIG. 1. Adjustable table drainage apparatus. This apparatus allows patient's head to be lowered to any position, as well as side to side adjustment, affording excellent bronchial drainage.

In the milder or moderately severe cases, postural drainage will usually suffice to completely empty the bronchial dilatations and prevent the disease from progressing in its severity or complications from developing. On our bronchiectatic service at this hospital we use a so-called "adjustable table drainage apparatus" (figure 1) and a "Jackknife drain" (figure 2), both of which are very useful and efficient in postural drainage. For the

past four months we have used a Singer multiposition bed which has been very useful in obtaining postural drainage in both pulmonary abscess and bronchiectasis cases. This multiposition bed has been especially advantageous for patients too sick to use the other methods of postural drainage.



Fig. 2. To illustrate Postural bar drain. This easily constructed apparatus affords drainage in the satisfactory bronchial drainage and has been preferred by most ambulant patients (Fig. 1).

Not infrequently, however, cases are seen that require bronchoscopic procedure as a therapeutic procedure. These cases fall into three main groups as follows:

1. Cases in which the purulent secretion cannot be completely drained satisfactorily, either to the thick nature of the secretion or to the weakness of the patient.

2. Cases in which persistent uncontrollable hemorrhage.

3. Cases which develop a pneumonitis about their bronchiectatic cavities, resulting usually from causes mentioned in 1. (See figures 3, 4, and 5.)

Included in the 200 cases of bronchiectasis which the writer has reviewed were 45 cases, 25 per cent, which required therapeutic bronchoscopic aspira-

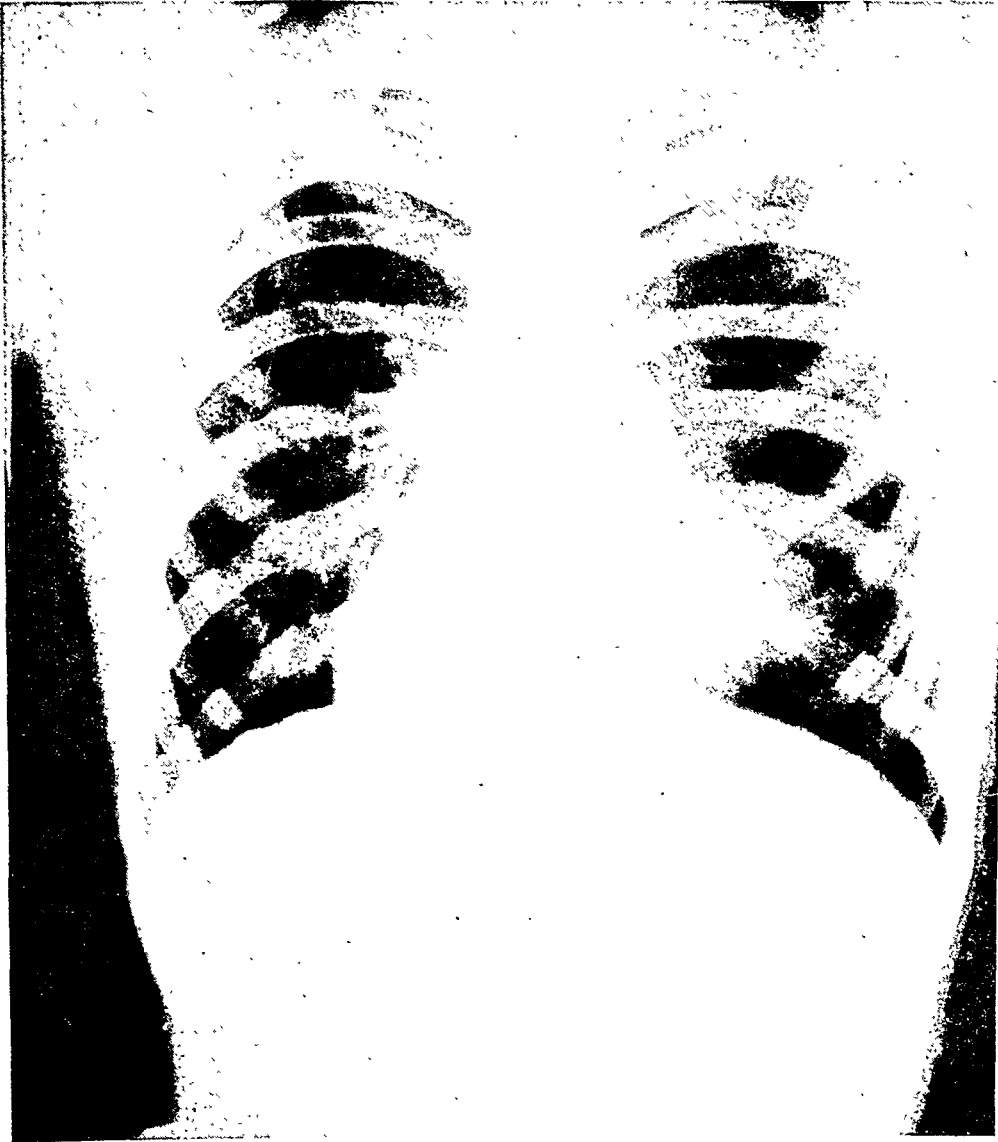


FIG. 3. Localized pneumonitis in right base, surrounding bronchiectatic dilatations. Patient discharged as "clinically cured" after several bronchoscopic aspirations combined with daily postural drainage.

tions. Of these 45 cases there were 24 which would definitely fall into group one, four cases into group two and 13 cases into group three. Many other patients were treated bronchoscopically with a view to hastening improvement and shortening the period of hospitalization, although we could not consider bronchoscopy as absolutely essential as a therapeutic measure.

We feel that bronchoscopy in the early milder cases may be beneficial as an aid in restoring the mucous membrane and its cilia to normality, thus preventing a progression of the disease and sometimes resulting in a clinical cure.

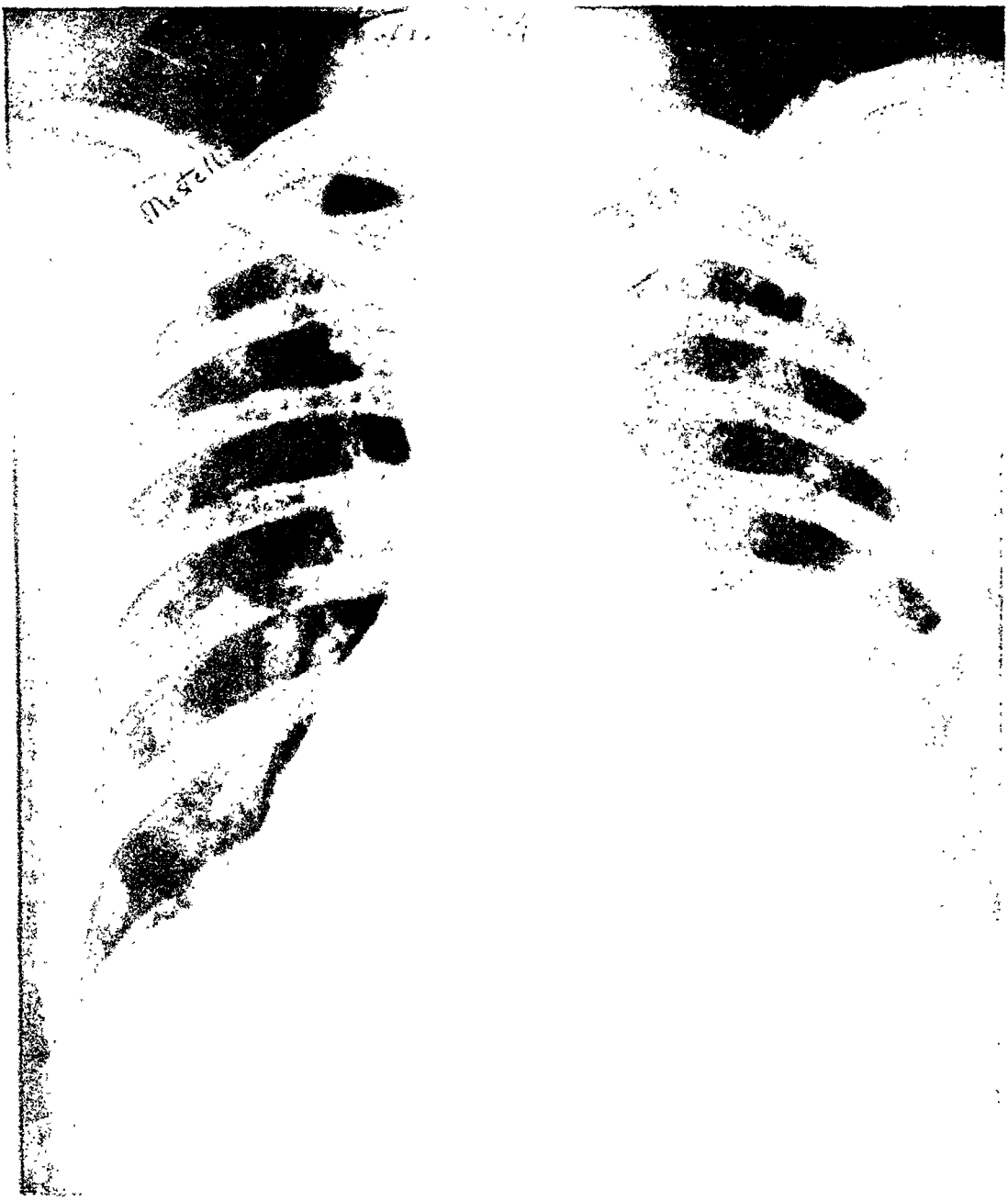


FIGURE 1. Two chest X-rays showing the area of the bronchiectasis, right 10-13 (Fig. 2), history, bronchiectasis.

Bronchoscopy is important and very beneficial to group one and group two cases, materially changing the aspect of a case from one of hopelessness to one of clinical improvement. Cases admitted a year ago are now able to be up and about in a short time and

soon feel much better, with an improvement in appetite and a gain in weight. A few bronchoscopic aspirations usually suffice in group one cases, following which they are usually able to drain sufficiently well by our ordinary methods of postural drainage. Group two cases usually have repeated small

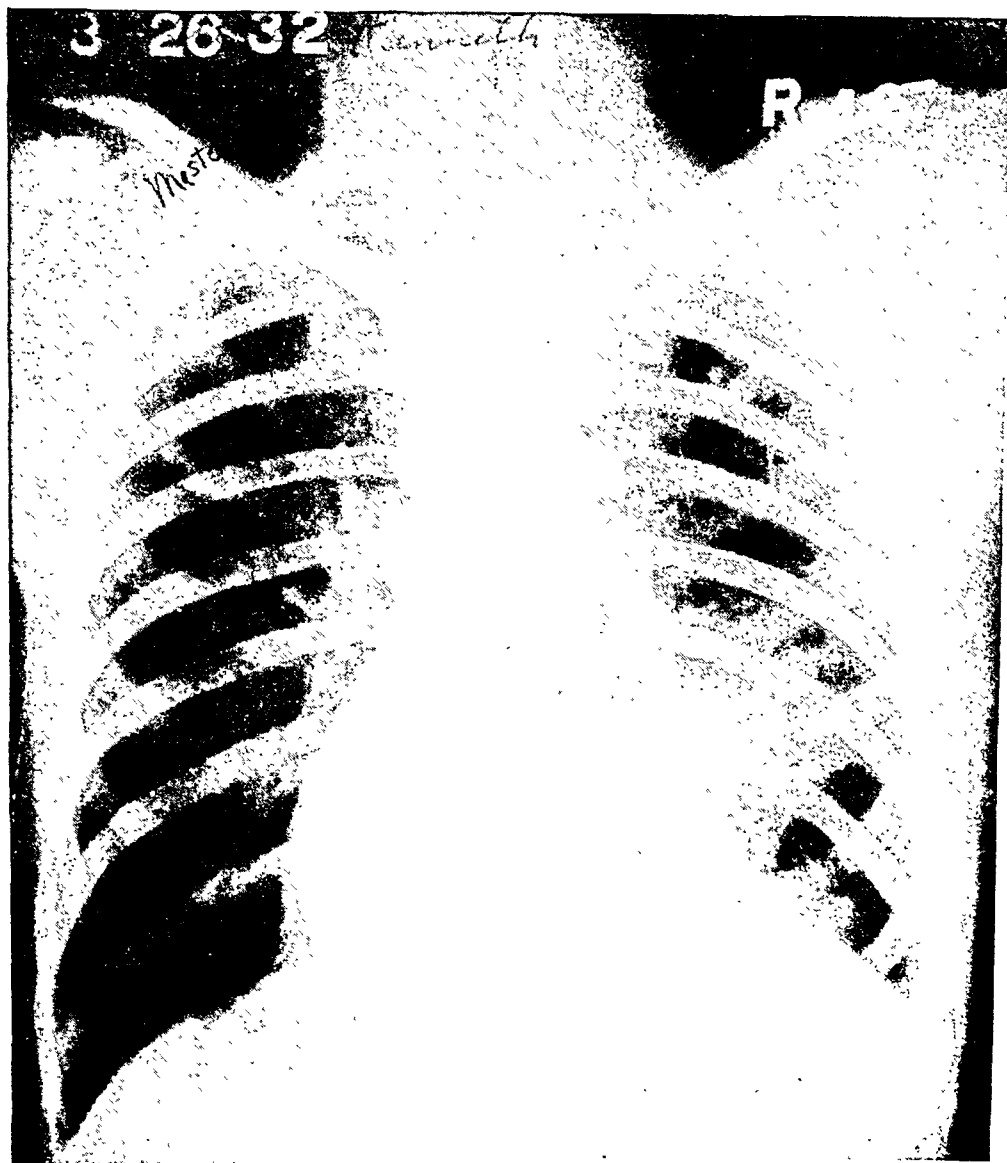


FIG. 5. X-ray of the same patient seven days later, showing the improvement following four bronchoscopic aspirations.

hemorrhages, though large hemorrhages have been reported. The bronchoscopist can usually find the bleeding area, and cauterization with silver nitrate suffices to control the bleeding.

It is the type of case seen in group three that requires early and repeated bronchoscopic treatment. These cases in which a pneumonitis has devel-

oped about the bronchial dilatations often run a toxic course with a rather high temperature and are usually progressive in severity. The inflammatory reaction or pneumonitis is usually caused by retained secretions in a severe case of bronchiectasis; or it may develop about bronchiectatic abscesses. This spread of the infection and inflammatory reaction into the pulmonary tissue is a very serious complication and requires early active treatment with a view to preventing a further spread of the pneumonitis or possible pulmonary abscess formation. We have seen several cases in which the pneumonitis continued to spread until bronchoscopic drainage was instituted, and daily bronchoscopies have been necessary in an occasional case. Semi-weekly drainage is usually sufficient in these cases to stop the spread of the infection and to start resolution of the pneumonitis and clinical improvement. One of our severe cases developed a pneumonitis followed by a pulmonary abscess and died in spite of nearly all types of treatment, including repeated bronchoscopy. Figure 3 shows an early case of unilateral bronchiectasis with pneumonitis which cleared up after repeated bronchoscopic therapy, resulting in a clinical cure.

The following case history will illustrate a not unusual sequence of events in this serious disease and how important bronchoscopic therapy is in such cases. Similar cases have been not infrequently observed in this hospital in the past three years.

CASE HISTORY

Male, age 58, Retired Army Officer. Past history unimportant. Originally admitted to this hospital in 1920 for active pulmonary tuberculosis of the right upper lobe, he was readmitted for the same condition in 1921, and then later discharged as inactive as regards tuberculosis. In 1927 a diagnosis of "bronchiectasis, chronic, mild, both lower lobes," was added at this hospital. On March 11, 1932 he was readmitted to this hospital with temperature of 101° F., considerable cough and increased expectoration. He was drained posturally for nine days but his condition gradually became worse, the temperature mounted to 104° F., and the patient showed evidence of severe toxemia. A roentgenogram taken on March 19, 1932 showed considerable pneumonitis present about the large bronchiectatic dilatations (figure 4). He was given a therapeutic bronchoscopy on the morning of 3/20/32, and the temperature dropped to 99.4° F. at 4:00 p.m.; the general condition seemed much improved. About 60 c.c. of thick foul pus were aspirated from the right base at this bronchoscopy. The patient received daily therapeutic bronchoscopies on March 20, 21, 22 and 23. On the latter three days the temperature was normal in the mornings with a maximum rise to 99.6° F. in the evenings. Lessened amounts of pus were aspirated on each successive day and the patient's improvement was rapid and progressive. Further bronchoscopies were made on March 26, April 1 and 8. The patient felt very well and was temperature-free from March 24 until his discharge from hospital on April 10, 1932. Figure 5 is the roentgenogram of the chest on 3/26/32 and shows that considerable improvement had taken place since the roentgenogram on 3/19/32. Figure 6 shows that the pneumonitis had cleared on 4/8/32, two days prior to discharge from the hospital.

This patient was again admitted to the hospital on January 22, 1933, in about the same condition as on the March 1932 admission. He was given a therapeutic bronchoscopy on the day of admission. The report of the bronchoscopist was as follows:

"About 45 c.c. of pus were obtained from two cavities in the right lower lobe. The septum between the two cavities was markedly thickened and congested. Aspirated and silver nitrate applied." On January 23: "About 20 c.c. of pus found in right lower bronchus, septum much less thickened." Improvement was sudden and rapid, the patient being able to return home in a short time. He now returns to the hospital for weekly bronchoscopic therapy in addition to practicing daily postural drainage at home.

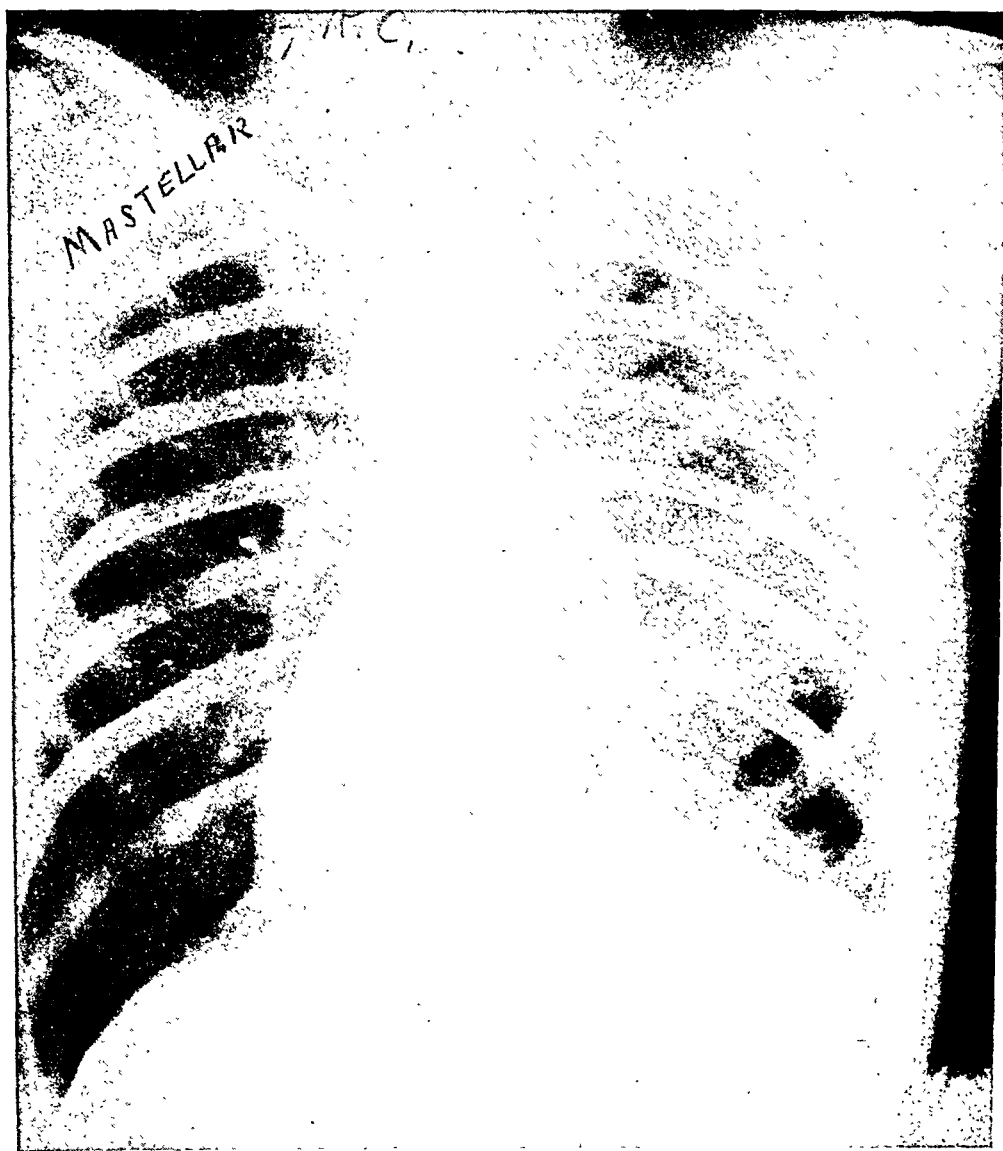


FIG. 6. Marked clearing of the pneumonitis, same patient, 4/8/32, following seven therapeutic bronchoscopic aspirations plus postural drainage several times daily.

CONCLUSIONS

Bronchoscopy is considered an important aid in the diagnosis of bronchiectasis. It is much more important and necessary from a therapeutic stand-

point, being the means by which hemorrhage may be controlled or purulent secretion aspirated in patients who are unable to drain sufficiently by our postural methods. Bronchoscopy's greatest efficacy in this disease is found in the treatment of those cases with a secondary pneumonitis about the areas of bronchiectasis. In these cases bronchoscopic aspiration may be the only effective method to prevent the spread of the inflammatory reaction with possible abscess formation and death.

BIBLIOGRAPHY

- GRAHAM, E. A.: Bronchoscopic and surgical treatments of pulmonary suppuration, *Am. Rev. Tuberculosis*, 1928, xvii, 33-41.
- BALLON, H., SINGER, J. J., and GRAHAM, E. A.: Bronchiectasis, *Jr. Thorac. Surg.*, 1931, 1, 154; 1932, i, 296, 397, 502-561.
- MARVIN, H. P.: Chronic bronchiectasis, *Mil. Surg.*, 1932, lxxi, 1-15.
- CLERF, L. H.: Peroral endoscopy, *Arch. Otolaryng.*, 1930, xi, 343-360.
- BALLON, D. H.: Some observations upon value of bronchoscopy in treatment of bronchiectasis, *Jr. Thorac. Surg.*, 1933, ii, 267-269.
- JACKSON, C.: *Bronchoscopy and esophagoscopy; a manual of peroral endoscopy and laryngeal surgery*, 1927, Saunders, Philadelphia and London.
- JACKSON, C.: Teaching bronchoscopy and esophagoscopy, *Arch. Otolaryng.*, 1928, vii, 1-12.
- MARVIN, H. P.: Bronchiectasis, its prevalence and importance. (To be published in an early issue of *The Medical Bulletin of the Veterans' Administration*.)

EDITORIAL

CORONARY SCLEROSIS

THE calamities associated with coronary sclerosis occupy a more dramatic and tragic place in the public consciousness today than the fatalities due to any other disease of mankind. It is not the fact that heart disease leads all other causes of death, but the sudden and often unanticipated demise of an individual with coronary sclerosis, which emphasizes the uncertain tenure of life. Scarcely a day passes but the papers chronicle the sudden death of one individual or of more than one who is preëminent in the social, political, or financial life of the community. The literature on the subject is so voluminous that a brief statement of its essentials seems justifiable.

It would appear that coronary sclerosis is on the increase, a fact as yet unproved and perhaps impossible to verify. Numerous judicial and experienced medical observers are convinced that angina pectoris and acute coronary occlusion are on the increase, and they insist that this increase is not merely an apparent one, due to increased ability of the medical profession to recognize these conditions. It is conceivable and even probable that angina pectoris, exclusive of acute coronary occlusion, has increased without any change in the incidence or degree of coronary sclerosis as a result of the increasing stress under which people live. It is noteworthy that the anginal syndrome often appears in people at a time when they have been subjected to a considerable period of mental stress.

Coronary sclerosis manifests itself in a variety of ways, the commonest of which is the syndrome of angina pectoris. In the absence of pain, it may indicate its presence by the occurrence of paroxysmal nocturnal dyspnea. The clinical picture of progressive myocardial failure, in the absence of angina pectoris or hypertension, may have its basis in coronary sclerosis. The syndrome of acute coronary occlusion may occur without any antecedent evidence that the heart was diseased. Some patients who have suffered such an accident may be remarkably free of cardiac symptoms after recovery from the acute attack. And finally, there is a group of patients who in life have never had signs or symptoms of coronary sclerosis, but who are found to have advanced degrees of coronary disease at death. Willius has designated this unrecognizable condition as occult coronary sclerosis.

The diagnosis of angina pectoris continues to offer difficulty to the medical profession. Mistakes are of two kinds: first, failure to recognize the syndrome; and second, interpretation of thoracic pain as angina pectoris when it is not. There are three characteristics of the anginal syndrome which constitute a diagnostic triad of the condition. 1. The distress is situated behind the sternum. The pain in angina pectoris may be felt else-

where in the thorax, in the neck, the jaws or the epigastrium, but if such pain is to be denoted angina pectoris, then the relationship of the symptoms must conform in all other respects to that characteristic of the disease. The term precordial pain is highly objectionable inasmuch as pain so described usually is in the apical region or in the left anterior axillary line and such pain rarely proves to be the result of coronary sclerosis. If distress on effort has its situation beneath the sternum, the presumption is that coronary disease is its cause; if the pain is in the left lateral thoracic wall, the burden is on the examiner to prove that it is angina pectoris. 2. A characteristic feature of angina pectoris is that the attack is precipitated by anything that increases cardiac work. These are, in order of importance, physical exertion, particularly walking, excitement, ingestion of food, or combinations of these factors. This essential relationship of cardiac overload to the onset of an attack is diagnostic only if the seizure stops in a few moments after the provocative factor ceases to operate. 3. The attack of angina pectoris is brief. The typical attack is over in a few minutes, seldom lasting longer than fifteen minutes. Attacks of substernal pain lasting an hour or more should always lead to the suspicion that coronary occlusion has occurred.

Angina pectoris is a diagnosis based on symptoms and not on physical signs. In from 20 to 30 per cent of patients the diagnosis must be made in spite of a negative physical examination, in the absence of any abnormality of the electrocardiogram, and without any help from roentgenographic examination of the heart. This fact assumes tremendous medicolegal importance in relation to individuals who are fraudulently seeking insurance or payments for disability. If the patient seeking insurance is dishonest enough to conceal symptoms of angina pectoris, no method of examination may disclose the existence of coronary sclerosis. If an individual seeking to establish a claim of disability feigns the classical symptoms of the disease, no medical examination may be able to prove the fraudulence of the claim.

The greatest confusion exists regarding the significance of the electrocardiographic findings in the diagnosis of angina pectoris and coronary sclerosis. Fully a third of the patients with angina pectoris have electrocardiograms that are normal in all respects. Except for the typical electrocardiographic pattern that follows acute coronary occlusion, there are no other electrocardiographic changes that positively denote coronary disease, nor will lack of changes exclude its presence. Tracings taken of patients in attacks of angina pectoris may contain transitory changes in the RS-T segment of the electrocardiogram that are almost positive evidence of insufficiency of the coronary circulation. Delays in conduction, either in the bundle of His or in the bundle branches, or a prolonged Q-wave in Lead III, as described by Pardee, are presumptive but not diagnostic evidence of coronary sclerosis. Inversion of the T-waves, except those that represent a relic of acute coronary occlusion, are not the result of chronic insufficiency

of the coronary circulation but are the result of associated cardiac pathologic changes, the commonest of which is hypertensive heart disease.

The results of treatment of coronary disease, although leaving much to be desired, compare favorably with the results of treatment of other degenerative diseases. The judicious use of nitroglycerin and amyl nitrite occupies an important place. The use of drugs of the xanthine group has afforded unmistakable relief to a number of patients. Attempts at surgical treatment of angina pectoris have been hampered by lack of knowledge of the pathways of pain from the heart, by lack of any evidence that nerve section or nerve block modified the underlying pathologic condition or the course of the disease, and by the risk of surgical procedures of the more formidable types. Fortunately the pathways of pain from the heart are becoming better understood, and surgical procedures for the relief of pain may be expected to increase in precision and effectiveness proportionately. Needless to say, such operations must be reserved for patients whose pain has remained intractable following adequate medical treatment. Total removal of the thyroid gland has been reported to afford relief to patients with angina pectoris, and this method of surgical treatment calls for further careful evaluation.

Finally, there is the most important consideration of rest. The prescription of rest should be most accurate and individualized in every case. It should be planned to produce adequate reduction of metabolic demands and of physical and mental stress.

We, as physicians, are implored to do something to reduce the ravages of coronary sclerosis. But how much can we do? After all, coronary sclerosis is a part of senescence, and senescence is as much a part of life as birth and growth, and just as inevitable. Pneumonia has been called the friend of the aged, and death from coronary disease has just as much right to that designation. Moreover, sudden death spares the patient the suffering and invalidism often associated with death from other causes. On the other hand, everyone would like to find a way to prevent death from coronary sclerosis in the fifth and sixth decades; but the tempo and demands of life for the ambitious do not lend themselves to easy adjustment. Now, more than ever before, life for the average individual is a contest and a battle of energy. This is as true of nations as it is of individuals. The person who decides to indulge in the luxurious attitude of "*dolce far niente*" is apt to find himself outdistanced. To ask people to give up their stress in life is like crying, "Peace, peace, when there is no peace." When the social structure and ideals of our civilization will allow individuals to live leisurely and to survive, then we may anticipate some amelioration of coronary sclerosis. Until then we must content ourselves with such make-shifts of relaxation and leisurely living as our struggle for existence will permit.

A. R. BARNES.

REVIEWS

Clio Medica: A Series of Primers on the History of Medicine. Edited by E. B. KRUMBHAR, M.D. *Volume X. Nutrition.* By GRAHAM LUSK, Sc.D., M.D., LL.D. xi + 142 pages; 11.5 x 17 cm. Paul B. Hoeber, New York. 1933. Price, \$1.50.

This is a little book no student of medicine, young or old, can afford to miss. It traces through the centuries the development of our knowledge of nutritional metabolism—with scholarly care, and with a balanced judgment of relative values which could be given only by a master in this field. The reader, however, is not kept in the pure ether of mental processes. The picturesque and personal sides of the great scientists' lives are woven into the tale; and there is still space for quotation, for honest admiration, for anecdotes by the way, for keen comments, for comparisons with the science of our day and its patrons. A lesser man might have written a valuable tome on this subject but it took a great man to write this little book.

M. C. P.

Diabetes Mellitus, A Handbook of Simplified Methods of Diagnosis and Treatment. By I. M. RABINOWITCH, D.Sc., M.D., C.M., F.R.C.P.(C.). xv + 246 pages; 15 x 21 cm. The Macmillan Co., of Toronto, Canada. 1933. Price, \$3.50.

The author's wide experience in the Clinic for Diabetes of the Montreal General Hospital has led him to feel that an effective treatment for diabetes must be simple, both for the patient to follow and for the physician to control. One of the chief purposes of his book is to portray a method of treatment, in which the patient need know very little of food values and can substitute household measures and portion models for scales, and which the physician can control without determinations of blood sugar or alkali reserve. Only by such simplifications does the author believe that a good average of results can be obtained in the treatment of diabetics in general practice. Conceding that ideal treatment would involve more exact determinations, he does not feel that ideal treatment is capable of wide application outside of hospitals.

The methods used for instructing the patient in the measurement of the diet are ingenious and practical. The descriptions of the tests for sugar and of the procedures for the differentiation of glucose from other urinary reducing substances are clear and detailed. It seems to the reviewer, however, that in advocating the fermentation test as a quantitative procedure, instead of a titration method, the author is not simplifying but complicating the physician's task. It seems unwise also to advocate so much reliance upon urinary sugar and not to stress more than is done the fact that in a very large number of cases a heightened renal threshold permits marked hyperglycemia to exist without glycosuria.

The author employs a high carbohydrate-low calorie diet. An average adult diet would contain approximately 275 grams carbohydrate, 45 grams fat, and 80 grams protein, yielding about 1,800 calories. A portion of the carbohydrate allowance is often given in sweets such as jams and marmalade. On the other hand, fats are severely restricted. The patient's weight is kept at about five pounds below the normal for the age, sex, and height as determined by a formula. Insulin is employed when, in spite of this maintenance diet, sugar persists in the urine or hyperglycemia exists. The results of this system of treatment in the author's clinic have proved very satisfactory. These results are contained in other publications but are not included in this book.

There are brief chapters on the various clinical types of diabetes, its complica-

tions, and its relation to arteriosclerosis, gangrene, tuberculosis, thyroid disease, eye lesions, skin lesions, etc.

The book is not written primarily for internists but for general practitioners as well. It has been developed from the author's lectures to fourth year students. It is short, clear, definite, and practical. If in some respects the author's opinions seem radical, they are the more stimulating. For physicians who wish to give a trial to the author's theory of the dietetic treatment of diabetes, his book will serve as an excellent manual. It is for this purpose that it was written. Perhaps at some later date the author will collect in another volume the data which would be of interest to those who would wish critically to analyze his results.

M. C. P.

The Colon, Rectum, and Anus. By FRED W. RANKIN, B.A., M.A., M.D., F.A.C.S.; J. ARNOLD BARGEN, B.S., M.D., M.S. in Medicine, F.A.C.P.; and LOUIS A. BUIE, B.A., M.D., F.A.C.S. 812 pages; 435 illustrations. W. B. Saunders Company, Philadelphia. 1932.

This monograph is based on the large experience of The Mayo Clinic. Though written largely from the surgical point of view, it contains a great deal of interest and of value to the internist. This is especially true of certain chapters, notably those on granulomatous diseases, chronic ulcerative colitis, parasitic diseases, colonic manifestations of systemic origin, and functional obstructive disorders. Of these, the chapter on ulcerative colitis is particularly instructive and presents in a very thorough manner not only the clinical and pathological aspects of the disease and its complications but also an admirable summary of the investigations which have led Borgen to attribute etiological importance to a diplococcus. The description of his technic will be of interest to those attempting to confirm his work. The other medical chapters contain less evidence of originality. On the other hand, the chapters on the neoplasms, benign and malignant, of the colon and rectum are important contributions to the literature of this subject. Careful studies are presented of the clinical symptoms and signs, of roentgenological methods of investigation and of mortality. The various operative procedures are carefully evaluated.

The book is for the most part clearly written and very well illustrated. It will be an important reference volume for the internist as well as the surgeon.

M. C. P.

The Psychological Effects of Oxygen Deprivation (Anoxemia) on Human Behavior. By ROSS C. McFARLAND, Ph.D., Columbia University. 127 pages. Columbia University Press, New York. 1932. Price, \$1.50.

This monograph thoroughly discusses a problem which not infrequently comes to the attention of general physicians, especially in this age of aviation when persons suffer from the lack of oxygen as the result of high altitudes.

McFarland completely reviews the literature, gives a bibliography of 184 items, and discusses the experimental work carried out. His experimentations conclusively show the effects of oxygen upon human behavior. "Climate seems to have an important influence in determining the character and productiveness of a people as well as their physical characteristics. . . . The mental and emotional differences between the races of climatic extremes are as striking as the physiological and cultural productiveness."

Simple sensory and motor responses are not seriously impaired until extreme anoxemia is present. Volitional reactions are more easily impaired under acute anoxemia and loss of motor control is then marked although there are great individual differences. Loss of memory occurs very early, and the effect of diminished oxygen upon attention is very definite. The higher mental processes are impaired

and the basic patterns of personality can be obtained. Emotional extremes are more easily induced in anoxemia. "The results indicate clearly that personality is in the final analysis dependent upon the physio-chemical processes and that more thorough or profound knowledge concerning human behavior may be obtained by combining psychological and biochemical research."

J. L. McC.

Bacterial Infection with Special Reference to Dental Practice. By J. L. T. APPLETON, JR., B.S., D.D.S., Professor of Microbiology and Bacteriopathology, The Thomas W. Evans Museum and Dental Institute, School of Dentistry, University of Pennsylvania. Second edition. 654 pages with 122 engravings and 4 colored plates. Lea and Febiger, Philadelphia. 1933.

The general plan of this edition is very similar to that of the first. The book is divided into three parts. The first deals briefly with the morphology, physiology, and classification of bacteria, with their relation to their environment and with the action of chemicals upon them. The second part discusses rather thoroughly the subjects of infection and immunity. The third is devoted to various infections of the oral cavity. The book, however, has been in large part rewritten and much new material has been added. The second part has been much enlarged and the order in which the various topics are discussed has been rearranged. The treatment of oral hygiene has been extended and an entire chapter has been given to its discussion. The third part shows considerable revision and several new chapters have been added. The chapter originally given over to the discussion of clinical bacteriology has been divided and the several parts each appended in its appropriate place. A very useful list of references is given. The purposes of this book, as stated by the author, are: (1) "To aid the reader to form a comprehensive concept of infection"; and (2) "To point out wherever a knowledge of infection will help the dentist in understanding or solving his problems." These purposes would seem to be adequately met. The book is primarily of value to the dental student and the dentist. However, much of the third section should also be of interest to the physician.

F. W. H.

COLLEGE NEWS NOTES

Acknowledgment is made of the following gifts of publications to the Library by members of the College:

Dr. I. D. Bronfin (Fellow), Denver, Colo.—one reprint;
Dr. Philip B. Matz (Fellow), Washington, D. C.—one reprint;
Dr. Adolph Sachs (Fellow), Omaha, Nebr.—one reprint;
Dr. John W. Shuman (Fellow), Los Angeles, Calif.—one reprint;
Dr. Martin J. Synnott (Fellow), Montclair, N. J.—one reprint;
Dr. William H. Walsh (Fellow), Chicago, Ill.—one reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—one reprint.

At the Annual Meeting of the Medical Society of Virginia, during October, Dr. F. H. Smith (Fellow), Abingdon, Va., was made President-Elect, and Dr. James K. Hall (Associate), Richmond, Va., was elected a Vice-President.

Dr. John I. Marker (Fellow), Davenport, Iowa, was elected President of the Southeastern District Medical Society of Iowa during October, 1933.

Dr. Edward M. Green (Fellow) has resigned as Superintendent of the Harrisburg State Hospital, Harrisburg, Pa., after sixteen years of service in that capacity.

The City of Philadelphia, Trustee under the will of John Scott of Edinburgh, through its Board of Directors of City Trusts, has awarded The John Scott Medal to George Richards Minot in recognition of his work for the development of the liver treatment of pernicious anemia.

On October 23, 1933, Dr. Minot gave the first Jessie Horton Koessler Lecture of the Institute of Medicine of Chicago, his subject being "Anemia: Etiology and Treatment"; he also gave a lecture on this subject before the Cleveland Academy of Medicine on November 17, 1933.

Dr. Walter Freeman (Fellow), Washington, D. C., resigned December 1, 1933, as Director of Laboratories at St. Elizabeth's Hospital, and will devote himself to university and clinic work and to the private practice of neurology. Dr. Freeman addressed the Montgomery Co. (Ohio) Medical Society at Dayton recently on "Psychological Plagues." He was recently reelected Secretary of the Section on Nervous and Mental Diseases of the Medical Society of the District of Columbia. His present address is 1726 Eye Street, Washington, D. C.

Dr. George A. Pemberton Wright (Fellow), formerly of Kingston, Jamaica, is now located in Delancey, Guernsey, Channel Islands.

Dr. Albert E. Russell (Fellow), formerly of the United States Bureau of Mines, Washington, D. C., is now in charge of the public health and medical program of the

Tennessee Valley Authority, Knoxville, Tenn. Programs are being organized for malaria control, pellagra prevention, trachoma clinics, venereal disease clinics, tuberculosis, maternal and child welfare.

Dr. J. C. Meakins (Fellow), Montreal, and Dr. Cyrus C. Sturgis (Fellow), Ann Arbor, Mich., will be guest speakers at the Dallas Southern Clinical Society meeting, March 26 to 30, 1934.

Dr. Adolph Sachs (Fellow), Omaha, Nebr., was the first President of the newly organized Omaha Mid-West Clinical Society—"to bring post-graduate opportunities to the back door of the Physicians for the least cost." The first Annual Assembly of this organization was held October 30 to November 3, 1933, in Omaha. Among guest speakers were the following Fellows of the College: Dr. James B. Herrick and Dr. Julius H. Hess, both of Chicago.

ERRATUM.—In the ANNALS OF INTERNAL MEDICINE for December 1933, page 739, line 27, *mercurial* should read *compound* or *molecule*.

OBITUARIES

DR. JOHN C. S. LAPPEUS

On November 17, 1933, occurred the death of Dr. John C. S. Lappeus, of Binghamton, N. Y., following a short period of illness.

Dr. Lappeus was born in 1878 in Hornellsville, N. Y., now known as Hornell. He received his preliminary education at the Keystone Academy, Factoryville, Pa., and was granted his degree of M.D. in 1904 by the University of Buffalo School of Medicine. He was licensed to practice in both New York and Pennsylvania. For many years he was Attending Physician and member of the staff of the City Hospital, Lourdes Hospital and the Susquehanna Valley Home, all of Binghamton. He was a member of the staff on health education of the Binghamton Public Schools, a member of the Binghamton Academy of Medicine, the Broome County Medical Society, the New York State Medical Society and the American Medical Association. On December 30, 1926, he was elected to Fellowship in the American College of Physicians.

The American College of Physicians, in common with other professional and lay organizations, to many of which Dr. Lappeus belonged, has lost in his death a very able, loyal, earnest and progressive worker.

H. D. MARVIN, M.D., F.A.C.P.,

Binghamton, N. Y.

DR. FRANK PERKINS KEYES

Dr. Frank Perkins Keyes (Associate), Brooklyn, N. Y., died suddenly August 18, 1933, at Sudbury, Vt., of cerebral hemorrhage and diabetes mellitus.

Dr. Keyes was born February 3, 1857. He graduated from the Long Island College Hospital in 1888 and practiced medicine, therefore, for more than fifty years. After graduation, he became assistant to the late Dr. Stephen Edward Fuller, who was a surgeon. He continued this work until Dr. Fuller's death, and then continued general practice, doing some surgical work. He belonged to the type of "old fashioned doctors"; he brought common sense and general ability to his problems. He was quiet and unassuming but held in the highest esteem by his patients. His unusual kindness and sympathy were the outstanding features of his character and practice.

Dr. Keyes was a member of the Medical Society of the County of Kings, the New York State Medical Society, a Fellow of the American Medical Association, and had been an Associate of the American College of Physicians from its beginning.

DR. NOBLE PRICE BARNES

Dr. Noble Price Barnes (Fellow), Washington, D. C., died November 26, 1933; aged 62 years.

Dr. Barnes graduated from the Baltimore Medical College in 1893. He occupied the Chair of Pediatrics in the National Medical College, which later became the George Washington University Medical School. He taught *Materia Medica* in both the Dental and Medical Departments of George Washington University.

Dr. Barnes was a former President of the Medical Association of the District of Columbia, a former Secretary, President and member of the Board of Governors of the American Therapeutic Society, an organizer and former President of the Washington Medical and Surgical Society, and was one of the first Fellows of the American College of Physicians, having been elected in 1916. He was a delegate to the United States Pharmacopoeia Convention in 1930.

"His generous spirit and geniality will be missed by all with whom he came in contact."

WALLACE M. YATER, M.D., F.A.C.P.,
Governor for the District of Columbia.

ABSTRACT OF MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

December 3, 1933

The Board of Regents of the American College of Physicians met at the College Headquarters at Philadelphia at 10:30 a.m., December 3, 1933; presided over by the President, Dr. George Morris Piersol.

The following members of the Board of Regents were present: Dr. George Morris Piersol, Dr. Charles G. Jennings, Dr. James H. Means, Dr. Jonathan C. Meakins, Dr. William D. Stroud, Dr. William Gerry Morgan, Dr. James Alex. Miller, Dr. Sydney R. Miller, Dr. David P. Barr, Dr. James B. Herrick, Dr. Clement R. Jones, Dr. S. Marx White, Dr. Walter L. Bierring, Dr. John H. Musser, Dr. O. H. Perry Pepper, Dr. Francis M. Pottenger, Dr. Luther F. Warren, Dr. Maurice C. Pincoffs and Dr. Ernest B. Bradley. Dr. Charles H. Cocke, a member of the Committee on Credentials, was present as a guest, and the Executive Secretary, Mr. E. R. Loveland, acted as Secretary of the meeting.

The Executive Secretary read abstracted Minutes of the preceding meeting of the Board of Regents at Montreal, February 10, 1933, which were approved as read.

President Piersol commented briefly concerning the fact that the work of the College had been going along in a suitable manner and that no previous meeting of the Board of Regents, or of the Executive Committee, had seemed necessary, especially in view of the desirability of economy in the administration of the College.

REPORT OF THE SECRETARY-GENERAL

Dr. William Gerry Morgan, Secretary-General, presented the following communications:

A letter from the Chairman of the Committee on Cost of Current Medical Periodicals, thanking the College for its endorsement and assistance in their recent efforts to reduce and stabilize subscription prices of German periodicals particularly;

Two communications from Fellows applying for reinstatement. By resolution, Dr. Charles Jack Hunt, New York, N. Y., and Dr. Eugene A. Gilbert, Chattanooga, Tenn., were reinstated as Fellows of the College;

A number of letters from Fellows and Associates concerning resignations. By individual resolution, the following resignations were accepted:

Fellows:

I. Hope Alexander, Pittsburgh, Pa.

John B. Hawes, 2nd, Boston, Mass.

Associates:

Roderick E. Albright, Allentown, Pa.

James W. Bruce, Louisville, Ky.

David B. Davis, Grand Rapids, Mich.

Charles A. Howland, Schenectady, N. Y.

Glendon R. Lewis, Syracuse, N. Y.

John C. E. Nielsen, Los Angeles, Calif.

E. A. Sutherland, Madison, Tenn.

A number of letters from Fellows and Associates concerning fees and dues, which were acted upon individually according to merits of the cases and provisions of the By-Laws.

Dr. William Gerry Morgan, Secretary-General, then read the following list of deaths reported to the College since the last meeting of the Board of Regents:

Fellows:

S. Franklin Adams, New York, N. Y.	September 28, 1933
Neil Andrews, Oshkosh, Wis.	March 10, 1933
Noble P. Barnes, Washington, D. C.	November 26, 1933
William R. Bathurst, Little Rock, Ark.	August 30, 1933
John S. Davis, University, Va.	September 21, 1933
George J. Eckel, Buffalo, N. Y.	October 29, 1933
Thomas Wray Grayson, Pittsburgh, Pa.	May 16, 1933
Neal L. Hoskins, Detroit, Mich.	July 21, 1932
John C. S. Lappeus, Binghamton, N. Y.	November 17, 1933
Martin J. Larkin, Toledo, Ohio	March 11, 1933
R. E. Loucks, Detroit, Mich.	June 5, 1933
Henry G. Mehrrens, San Francisco, Calif.	February 28, 1933
Edward W. Meis, Sioux City, Iowa.	December 7, 1932
William H. Mercur, Pittsburgh, Pa.	July 16, 1933
Charles Howard Miller, San Leandro, Calif.	February 2, 1933
Franklin E. Murphy, Kansas City, Mo.	February 20, 1933
Edward O. Otis, Exeter, N. H.	May 28, 1933
Judd Campbell Shellito, Independence, Iowa	April 16, 1933
W. Blair Stewart, Atlantic City, N. J.	July 11, 1933
Shannon Laurie Van Valzah, Denver, Colo.	July 11, 1933
John Bloss Wolfe, Wilkes-Barre, Pa.	June 1, 1933

Associates:

Raymond J. Harris, Philadelphia, Pa.	August 9, 1933
Frank Perkins Keyes, Brooklyn, N. Y.	August 18, 1933
Thomas J. McKinney, Champaign, Ill.	May 27, 1933
W. F. Mitchell, Superior, Nebr.	June 3, 1932
Walker Eugene Stallings, Denver, Colo.	May 6, 1933

By resolution, the following were discontinued from the roll of the College:

Ray C. Barrick (Associate), Joliet, Ill.
 George Henry Benton (Fellow), Coral Gables, Fla.
 Julian R. Blackman (Fellow), Salt Lake City, Utah
 James E. Harvey (Associate), Pasadena, Calif.
 Finn Koren (Associate), Watertown, S. D.

REPORT OF THE GENERAL CHAIRMAN OF THE CLINICAL SESSION

Dr. James B. Herrick, General Chairman of the Eighteenth Annual Clinical Session, reported upon preliminary arrangements made by him as General Chairman of the Session. He has appointed Dr. Arthur R. Elliott as Chairman of the Committee on Clinics, and has selected certain other committee members. In conference with Dr. Elliott, it has been decided that only the medical schools and the teaching hospitals will be called upon to coöperate in presenting clinics. A member of the Committee on Clinics has been selected from each of these medical schools and hospitals, including the Graduate School of Medicine of the University of Chicago, the University of Illinois College of Medicine, Northwestern University Medical School, Loyola University School of Medicine, Rush Medical College, Presbyterian Hospital, Michael Reese Hospital, St. Luke's Hospital, Mercy Hospital, Children's Memorial Hospital

and the Cook County Hospital. Dr. Herrick particularly asked for suggestions from the Board of Regents concerning the number of guest clinicians that should be invited.

In connection with an entertainment program for the visiting women, Dr. Herrick said that the Ladies Committee would provide headquarters at the hotel for the registration and reception of the ladies. A directory of interesting places and events will be furnished, and possibly one or two organized trips will be arranged.

Dr. Herrick discussed the names of several men of national reputation as the chief speaker on the occasion of the annual banquet. In connection with publicity for the meeting, Dr. Herrick reported that an article on "Chicago as a Medical Center" had been prepared and submitted to the Editor of the *ANNALS OF INTERNAL MEDICINE* for publication. There was general discussion of the subject of publicity concerning the program. It was the consensus of opinion of the Board of Regents that increased effort should be made toward improving the character and scope of the publicity concerning the scientific program. The Executive Secretary was called upon to explain the present system of promoting publicity, which briefly has been as follows: a local committee of approximately five members, all physicians and Fellows of the College, has been selected to coöperate with various news agencies and local reporters. Preceding the meeting, abstracts of as many papers as possible are secured, and these are further translated for the use of the reporters. During the meeting at least one of these physicians is in attendance at each session, and thereafter translates the papers in understandable language to the reporters, thus giving the reporters invaluable aid and assuring to the College a better type of publicity than could be secured from lay reporters. It has been customary to have in attendance representatives from Science Service, the Associated Press, the United Press, and the local newspapers. A regular headquarters office with typewriters and a secretary has been provided.

There was general discussion concerning the matter of guest clinicians, some expressing the opinion that most of the members would be more particularly interested in seeing what is being done by the men in Chicago, although the addition of a few guest clinicians from outside of Chicago would undoubtedly be very appropriate and would attract additional attendants to the clinics. It was further stated that the clinical program should be as broad as possible, and that the work in some of the great laboratories in Chicago should particularly be shown.

Dr. Herrick discussed the arrangements for the Smoker, the first evening of the Session, expressing the desire to have an entertaining though dignified program.

Dr. George Morris Piersol, President, distributed the preliminary copy of the program for the General Sessions, for which he is responsible. He had selected, for the most part, Fellows of the College, expressing the opinion that there are an adequate number of eminent authorities within the College membership without inviting a large number of guests. The speakers have been selected from all parts of the country, and the program will include a broad scope of subjects. Special papers have been arranged for those interested in pediatrics, neurology, psychiatry and various other specialties affiliated with internal medicine. Radiology will be taken care of largely through special clinics this year.

Dr. James H. Means expressed the opinion that the addition of one or two distinguished foreign guests always adds much to the meeting.

Mr. E. R. Loveland, Executive Secretary, reported that the usual business arrangements had been made for the Clinical Session, that the Palmer House had been selected for headquarters, where there would be adequate facilities for the general headquarters, for the exhibits, for the General Sessions and for accommodation of practically all physicians who may desire to stay at the headquarters hotel.

REPORT OF THE COMMITTEE ON CREDENTIALS

Dr. Sydney R. Miller, Chairman of the Committee on Credentials, reported that his Committee had examined carefully the credentials of all candidates for Fellowship and Associateship. Of 55 candidates for Fellowship, 39 were recommended for election to Fellowship, 1 was recommended for election first to Associateship, 6 were held as Associates, 5 were deferred for further information and 4 were recommended for rejection. Of the 110 candidates for Associateship, 92 were recommended for election to Associateship, 6 were deferred for more information and 12 were recommended for rejection.

Dr. Miller then presented the following list of 40 candidates recommended to the Board of Regents for election to Fellowship: (1, indicates proposer; 2, seconder; 3, endorser).

California

Dudley Wayne Bennett, San Francisco.

1. Ernest H. Falconer; 2. Irwin C. Schumacher; 3. William J. Kerr and Hans Lisser.

Louis Henry Fales, Livermore.

1. Audley O. Sanders; 2. M. B. Marcellus; 3. William J. Kerr and Hans Lisser.

Arthur Max Hoffman, Los Angeles.

1. Harold H. Smith; 2. Henry H. Lissner; 3. Egerton Crispin.

Earl Oriol Gregor Schmitt, San Jose.

1. D. Schuyler Pulford; 2. Albert H. Rowe; 3. Walter L. Bierring and Hans Lisser.

Milo Kenney Tedstrom, Santa Ana.

1. Roland Cummings; 2. R. Manning Clarke; 3. Egerton Crispin.

Connecticut

William Haviland Morriss, Wallingford.

1. Arthur Bliss Dayton; 2. George Blumer; 3. Henry F. Stoll.

Illinois

David Oscar Nathaniel Lindberg, Decatur.

1. Cecil M. Jack; 2. O. O. Stanley; 3. Samuel E. Munson.

Edgar McLean Stevenson, Bloomington.

1. Gerald M. Cline; 2. John R. Vonachen; 3. Samuel E. Munson.

Indiana

William G. Crawford, Terre Haute.

1. Herman M. Baker; 2. Edgar F. Kiser; 3. Robert M. Moore.

Leon G. Zervas, Indianapolis.

1. J. A. MacDonald; 2. Edgar F. Kiser; 3. Robert M. Moore.

Kentucky

John Sharpe Chambers, Lexington.

1. Charles N. Kavanaugh; 2. W. S. Wyatt; 3. Ernest B. Bradley.

Louisiana

Robert Theodore Lucas, Shreveport.

1. Arthur A. Herold; 2. T. P. Lloyd; 3. Joseph E. Knighton.

Maine

John O. Piper, Waterville.

1. E. H. Drake; 2. E. R. Blaisdell; 3. E. W. Gehring.

Michigan

Roy DeVaughan Metz, Detroit.

1. Alpheus F. Jennings; 2. Herman H. Riecker; 3. James D. Bruce.

John William Towey, Powers.

1. J. A. Myers; 2. Stuart Pritchard; 3. James D. Bruce.

Minnesota

Robert Bernard Radl, Minneapolis.

1. J. A. Myers; 2. Arnold S. Anderson; 3. S. Marx White.

New York

Alvan LeRoy Barach, New York.

1. Joseph H. Barach; 2. Walter W. Palmer; 3. James Alex. Miller and Robert A. Cooke.

Clifton H. Berlinghof, Binghamton.

1. H. B. Marvin; 2. Walter A. Baetjer; 3. Robert A. Cooke.

George Walter Cramp, Brooklyn.

1. Frank Bethel Cross; 2. Charles Eastmond; 3. Luther F. Warren and Robert A. Cooke.

Edward Percy Eglee, New York.

1. Grant Thorburn; 2. J. Burns Amberson; 3. James Alex. Miller and Robert A. Cooke.

Eugene Roland Marzullo, Brooklyn.

1. John B. D'Albora; 2. A. F. R. Andresen; 3. Luther F. Warren and Robert A. Cooke.

Foster Murray, Brooklyn.

1. Julian P. Dworetzky; 2. Eugene S. Dalton; 3. James Alex. Miller and Robert A. Cooke.

North Carolina

Coy Cornelius Carpenter, Wake Forest.

1. L. B. McBrayer; 2. William B. Dewar; 3. C. H. Cocke.

Frederick Moir Hanes, Durham.

1. Wingate M. Johnson; 2. T. C. Redfern; 3. C. H. Cocke.

Daniel Franklin Milam, Raleigh.

1. Verne S. Caviness; 2. Hubert B. Haywood; 3. C. H. Cocke.

James William Vernon, Morganton.

1. Wingate M. Johnson; 2. Coite L. Sherrill; 3. C. H. Cocke.

Oklahoma

Ben Hunter Cooley, Norman.

1. L. J. Moorman; 2. Wann Langston; 3. Lea A. Riely.

Hugh Gilbert Jeter, Oklahoma City.

1. J. T. Martin; 2. Arthur W. White; 3. Lea A. Riely.

Pennsylvania

Samuel Goldberg, Philadelphia.

1. John A. Kolmer; 2. Edward Weiss; 3. E. J. G. Beardsley.

Thomas Murphy McMillan, Philadelphia.

1. Olin S. Allen; 2. Alfred Stengel; 3. E. J. G. Beardsley.

James MacLaren Strang, Pittsburgh.

1. Frank A. Evans; 2. R. R. Snowden; 3. E. Bosworth McCready.

Texas

Robert Mitchell Barton, Dallas.

1. H. M. Winans; 2. G. E. Brereton; 3. C. T. Stone.

Medical Corps, U. S. Army

Major Frank Henry Dixon, Corozal, Canal Zone.

1. C. D. Brisc e; 2. J. F. Siler; 3. William M. James and Robert U. Patterson.

Medical Corps, U. S. Navy

Admiral Perceval Sherer Rossiter, Washington, D. C.

1. Charles E. Riggs.

Canada

Ontario

George K. Wharton, London.

1. George E. Brown; 2. L. G. Rowntree; 3. Jabez H. Elliott.

Quebec

James Bertram Collip, Westmount.

1. A. T. Henderson; 2. C. G. Sutherland; 3. D. Sclater Lewis.

Mexico

Ignacio Chavez, Mexico City.

1. Lee Rice; 2. Joe Kopecky; 3. C. T. Stone.

Francisco de P. Miranda, Mexico City.

1. Lee Rice; 2. Joe Kopecky; 3. C. T. Stone.

Siam

Edwin Charles Cort, Chiengmai.

1. Thomas R. Brown; 2. Ernest H. Gaither; 3. Henry M. Thomas, Jr.

On motion seconded and regularly carried, it was

RESOLVED, that the above 39 candidates, individually presented, shall be and are herewith elected to Fellowship in the American College of Physicians.

Dr. Miller then presented the following list of 93 candidates recommended for election to Associateship: (1, indicates proposer; 2, seconder; 3, endorser).

Arizona

Jesse Dewey Hamer, Phoenix.

1. Charles S. Kibler; 2. Samuel H. Watson; 3. W. Warner Watkins.

Arkansas

Elmer John Munn, El Dorado.

1. Fergus O. Mahoney; 2. George B. Fletcher; 3. Oliver C. Melson.

California

William Clifford Cooke, San Diego.

1. Clair L. Stealy; 2. Lyell C. Kinney; 3. Egerton Crispin.

Felix Cunha, San Francisco.

1. William J. Kerr; 2. Fred H. Kruse; 3. Hans Lisser.

Cullen Ward Irish, Los Angeles.

1. Stephen Smith; 2. Charles W. Thompson; 3. Egerton Crispin.

Raymond Arthur Sands, Santa Monica.

1. John V. Barrow; 2. Roland Cummings; 3. Egerton Crispin.

James Robert Sanford, Pasadena.

1. Robert Edward Ramsay; 2. F. M. Pottenger; 3. Egerton Crispin.

Rudolph Herbert Sundberg, San Diego.

1. Addison E. Elliott; 2. James F. Churchill; 3. Egerton Crispin.

Connecticut

Marcus Backer, Bridgeport.

1. Daniel P. Griffin; 2. George Blumer; 3. Henry F. Stoll.

Abe S. Brown, Waterbury.

1. John H. Foster; 2. J. Harold Root; 3. Henry F. Stoll.

Henry Caplan, Meriden.

1. Thomas P. Murdock; 2. Joseph I. Linde; 3. Henry F. Stoll.

John Cowles White, New Britain.

1. G. Gardiner Russell; 2. Orin R. Witter; 3. Henry F. Stoll.

District of Columbia

John Minor, Washington.

1. Alexander B. Moore; 2. Lester Neuman; 3. Wallace M. Yater.

Florida

Kenneth Phillips, Miami.

1. William Henry Watters; 2. C. F. Roche; 3. James B. Herrick.

Georgia

John Cox Wall, Eastman.

1. Thomas E. Rogers; 2. James A. Fountain; 3. Russell H. Oppenheimer.

Illinois

Stuart Welsh Adler, Rock Island.

1. William F. Schroeder; 2. Hugh A. Beam; 3. Samuel E. Munson.

Thomas Davis Masters, Springfield.

1. Frank Parsons Norbury; 2. Frank G. Norbury; 3. Samuel E. Munson.

Maxim Pollak, Peoria.

1. William Henry Walsh; 2. George W. Parker; 3. Samuel E. Munson.

Indiana

Harry Brandman, Whiting.

1. Paul H. Dietrich; 2. J. A. Teegarden; 3. Robert M. Moore.

James H. Stygall, Indianapolis.

1. Edgar F. Kiser; 2. John A. MacDonald; 3. Robert M. Moore.

Iowa

William Edward Ash, Council Bluffs.

1. Ernest Kelley; 2. A. A. Johnson; 3. Walter L. Bierring and Tom Bentley Throckmorton.

Robert N. Larimer, Sioux City.

1. John H. Peck; 2. A. C. Page; 3. Walter L. Bierring and Tom Bentley Throckmorton.

Theodore John Pfeffer, DeWitt.

1. J. Arnold Barga; 2. Henry W. Woltman; 3. George E. Brown, Tom Bentley Throckmorton and Walter L. Bierring.

Benjamin Franklin Wolverton, Cedar Rapids.

1. John H. Peck; 2. Addison C. Page; 3. Walter L. Bierring and Tom Bentley Throckmorton.

Kentucky

Benjamin Lane Brock, Waverley Hills.

1. Lawrason Brown; 2. Edgar Mayer; 3. Ernest B. Bradley.

Carl Hale Fortune.

1. Charles N. Kavanaugh; 2. George H. Wilson; 3. Ernest B. Bradley.

Louisiana

Thomas Everett Strain, Shreveport.

1. W. S. Kerlin; 2. T. E. Williams; 3. J. E. Knighton.

Clarence Hungerford Webb, Shreveport.

1. T. P. Lloyd; 2. C. P. Rutledge; 3. J. E. Knighton.

Massachusetts

Raymond Lathrop Barrett, Springfield.

1. George L. Steele; 2. Laurence D. Chapin; 3. J. H. Means and Roger I. Lee.

John A. Foley, Boston.

1. Soma Weiss; 2. William B. Castle; 3. J. H. Means and Roger I. Lee.

Allen Sheppard Johnson, Springfield.

1. Laurence D. Chapin; 2. George L. Steele; 3. J. H. Means and Roger I. Lee.

Egon Emil Kattwinkel, Auburndale.

1. Dwight O'Hara; 2. William D. Reid; 3. Roger I. Lee.

Jerome Andrew Whitney, Springfield.

1. George L. Steele; 2. Laurence D. Chapin; 3. James H. Means and Roger I. Lee.

Michigan

Russell L. Finch, Lansing.

1. Milton Shaw; 2. L. G. Christian; 3. James D. Bruce.

George Lawrence Leslie, Howell.

1. George A. Sherman; 2. Richard M. McKean; 3. James D. Bruce.

Harold Abraham Robinson, Detroit.

1. William G. Gordon; 2. Lawrence Reynolds; 3. James D. Bruce.

Harold Riche Roehm, Birmingham.

1. Walter M. Simpson; 2. Carl V. Weller; 3. James D. Bruce.

Ferdinand Ripley Schemm, Ann Arbor.

1. Cyrus C. Sturgis; 2. Carl V. Weller; 3. James D. Bruce.

Joseph Francis Whinery, Grand Rapids.

1. Joseph B. Whinery; 2. Thomas D. Gordon; 3. James D. Bruce.

Minnesota

Elmer Clarence Bartels, Duluth.

1. P. P. Vinson; 2. Fred W. Gaarde; 3. George E. Brown and E. L. Tuohy.

Vernon Lawrence Evans, Rochester.

1. James F. Weir; 2. George E. Brown; 3. Edward L. Tuohy.

Ross Martin Lymburner, Rochester.

1. F. A. Willius; 2. George E. Brown; 3. Edward L. Tuohy.

James Stuart McQuiston, Rochester.

1. George E. Brown; 2. Samuel F. Haines; 3. E. L. Tuohy.

Harold Conrad Ochsner, Rochester.

1. H. Milton Conner; 2. George E. Brown; 3. Edward L. Tuohy.

Edward George Thorp, Rochester.

1. F. W. Gaarde; 2. O. K. Maytum; 3. Edward L. Tuohy.

Mississippi

George Lamar Arrington, Meridian.

1. Noel C. Womack; 2. Felix J. Underwood; 3. G. W. F. Rembert.

Nevada

Lawrence Parsons, Reno.

1. John C. Ruddock; 2. William H. Leake; 3. Egerton Crispin.

New Jersey

Ferdinand Charles Dingel, East Orange.

1. John W. Gray; 2. George H. Lathrop; 3. W. Blair Stewart (deceased).

Paolo F. Liva, Lyndhurst.

1. Richard Edward Knapp; 2. Herman Trossbach; 3. W. Blair Stewart (deceased).

Carlyle Morris, Metuchen.

1. Frederick L. Brown; 2. F. C. Johnson; 3. W. Blair Stewart (deceased).

Joseph Reginald Pierson, Trenton.

1. Joseph T. Beardwood; 2. J. F. Pessel; 3. W. Blair Stewart (deceased).

New York

Victor W. Bergstrom, Binghamton.

1. H. B. Marvin; 2. John C. S. Lappeus (deceased); 3. James Alex. Miller and Robert A. Cooke.

Stephen H. Curtis, Troy.

1. Crawford R. Green; 2. Harry W. Carey; 3. Robert A. Cooke.

Maurice Coleman Harris, New York.

1. Samuel Weiss; 2. Robert Chobot; 3. Robert A. Cooke.

Warren F. Kahle, Larchmont.

1. Arthur F. Heyl; 2. Richard A. Kern; 3. O. H. Perry Pepper and Robert A. Cooke.

Max Mensch, Brooklyn.

1. Philip I. Nash; 2. Thomas J. Longo; 3. Robert A. Cooke.

Theresa Scanlan, New York.

1. C. F. Tenney; 2. Henry T. Chickering; 3. James Alex. Miller and Robert A. Cooke.

Isaac Shapiro, Schenectady.

1. Lester Betts; 2. Frank vander Bogert; 3. Robert A. Cooke.

George Widmer Thorn, Buffalo.

1. Nelson G. Russell; 2. Clayton W. Greene; 3. Allen A. Jones.

Max Trubek, New York.

1. Louis F. Bishop, Jr.; 2. Louis F. Bishop, Sr.; 3. James Alex. Miller and Robert A. Cooke.

North Carolina

George Curtis Crump, Asheville.

1. A. B. Craddock; 2. S. L. Crow; 3. C. H. Cocke.

Paul Allison Yoder, Winston-Salem.

1. Wingate M. Johnson; 2. P. P. McCain; 3. C. H. Cocke.

Ohio

Abel A. Applebaum, Toledo.

1. L. A. Levison; 2. John T. Murphy; 3. A. B. Brower.

Frank J. Doran, Cleveland.

1. Ralph K. Updegraff; 2. Henry J. John; 3. A. B. Brower.

Oregon

George Wilber Millett, Portland.

1. John H. Fitzgibbon; 2. Marr Bisailon; 3. Homer Coffen.

Pennsylvania

Nathan Blumberg, Philadelphia.

1. Joseph C. Doane; 2. Arthur C. Morgan; 3. E. J. G. Beardsley.

John Milnes Dyson, Hazleton.

1. David Riesman; 2. Charles H. Miner; 3. O. H. Perry Pepper and E. J. G. Beardsley.

Paul H. Parker, Jenkintown.

1. Joseph T. Beardwood; 2. H. L. Bockus; 3. William D. Stroud and E. J. G. Beardsley.

Floyd W. Stevens, Scranton.

1. Arthur E. Davis; 2. W. M. Donavan; 3. George Morris Piersol.

Elwood Wakefield Stitzel, Altoona.

1. E. Roland Snader, Jr.; 2. Augustus S. Kech; 3. E. Bosworth McCready.

Rhode Island

Henry Stephen Joyce, Providence.

1. Charles F. Gormly; 2. Guy W. Wells; 3. Alex. M. Burgess.

Clifton Briggs Leech, Providence.

1. Charles F. Gormly; 2. Guy W. Wells; 3. Alex. M. Burgess.

Harvey Elijah Wellman, Providence.

1. Charles F. Gormly; 2. Guy W. Wells; 3. Alex. M. Burgess.

Henry L. C. Weyler, Providence.

1. Charles F. Gormly; 2. Guy W. Wells; 3. Alex. M. Burgess.

Elihu Smith Wing, Providence.

1. John F. Kenney; 2. Charles F. Gormly; 3. Alex. M. Burgess.

Tennessee

Tolbert Clinton Crowell, Chattanooga.

1. Franklin B. Bogart; 2. Leopold Shumacker; 3. J. O. Manier.

Texas

Edgar Mullins Dunstan, Dallas.

1. Hugh Leslie Moore; 2. C. M. Grigsby; 3. C. T. Stone.

William J. Marr, Jr., Galveston.

1. George Herrmann; 2. George E. Bethel; 3. C. T. Stone.

Wendell Heath Paige, Brownwood.

1. Will S. Horn; 2. T. C. Terrell; 3. C. T. Stone.

Virginia

Vincent Joseph Dardinski, Clarendon.

1. Eugene R. Whitmore; 2. Walter Freeman; 3. Wallace M. Yater and J. Morrison Hutcheson.

Canal Zone

Ernst Thonnard-Neumann, Cristobal.

1. C. D. Briscoe; 2. Tomas Guardia; 3. William M. James.

Hawaii

Arthur Warren Duryea, Honolulu.

1. Harry L. Arnold; 2. A. G. Schnack.

Medical Corps, U. S. Army

Major Coleridge Livingstone Beaven, Washington, D. C.

3. Robert U. Patterson.

Major Samuel McPherson Browne, Washington, D. C.

1. Leon A. Fox; 2. Roger Brooke; 3. Robert U. Patterson.

Lt. Col. Frederick Hultman Foucar, San Francisco, Calif.

3. Robert U. Patterson.

Major Arthur Raymond Gaines, Denver, Colo.

1. William C. Pollock; 2. Everett L. Cook; 3. Robert U. Patterson.

Captain Horace Page Marvin, Denver.

1. William C. Pollock; 2. Everett L. Cook; 3. Robert U. Patterson.

Major Joseph Aaron Mendelson, Cheyenne, Wyoming.

3. Robert U. Patterson.

Medical Corps, U. S. Navy

Lt. Comdr. Lyle Jay Roberts, Washington, D. C.

1. Walter M. Anderson; 2. E. R. Stitt; 3. P. S. Rossiter.

U. S. Public Health Service

Olis Leon Anderson, Chelsea, Mass.

1. Albert D. Foster; 2. Frederick C. Smith; 3. J. P. Leake and Hugh S. Cumming.

*Canada**Alberta*

Percy Harry Sprague, Edmonton.

1. F. A. Willius; 2. Albert M. Snell; 3. Edward L. Tuohy.

*Korea**Chosen*

Zacharias Bercovitz, Pyengvang.

1. John Mark Lacey; 2. John V. Barrow; 3. Egerton Crispin.

On motion seconded and regularly carried, it was

RESOLVED, that the above 93 candidates shall be and are herewith elected to Associateship in the American College of Physicians.

REPORT OF THE TREASURER

The Treasurer, Dr. William D. Stroud, presented the financial report in the absence of Dr. Charles F. Martin, Chairman of the Finance Committee, who was unable

to attend because of illness. Dr. Stroud reported that five dividends had been received during the current year from closed banks in Pittsburgh, which reduces our balance in those institutions to \$11,900.00, whereas the original amount had been approximately \$37,000.00. The prospects are that there will be little or no loss from those banks. Dr. Stroud then reported that \$4,000.00, par value, Bonds of the City of Detroit had defaulted this year in their interest payments, but that the bonds had been deposited in accordance with the recommendations of our bank on a refinancing plan, which will probably result in the issuance of new bonds and the payment of past interest on the old bonds. The Treasurer also reported that since the last meeting of the Board of Regents, \$5,000.00 Province of Ontario bonds had been called, and that the proceeds were available for reinvestment. On motion seconded and regularly carried, it was

RESOLVED, that the Treasurer be authorized, after consultation with the Finance Committee, to reinvest proceeds of the \$5,000.00 maturity, Province of Ontario bonds, plus any other amounts not deemed necessary for the current expenses of the College.

In discussion that followed, it was suggested that possibly Government Bonds or Treasury Certificates would be appropriate securities in which to invest any surplus funds of the College at the present time.

The Treasurer then mentioned the fact that while the dues have been reduced practically 25 per cent for 1933 and our income thereby reduced approximately \$9,000.00, the number of delinquencies in dues has not been appreciably affected thereby, and that as many members are actually delinquent as when the dues were higher.

The Treasurer then presented two proposed budgets for 1934, one for the office of the General Chairman of the Annual Clinical Session and the other for the office of the President, in connection with his program for the Annual Clinical Session. These budgets covered expenses of secretarial service, honoraria to the banquet speaker, expenses for the publicity committee, the Ladies Entertainment Committee, traveling expenses for invited guest speakers, etc. These budgets were prepared in accordance with the directions of the Board of Regents at their meeting a year ago.

The Treasurer then presented financial reports prepared by the Executive Secretary. One report consisted of a comparison of the 1932 expenditures, the 1933 budget and the 1933 expenditures, with the months of November and December estimated. This statement disclosed that the total expenditures in 1932 amounted to \$61,376.58, that the budget for 1933 was reduced to \$50,686.67, and that the actual expenditures for 1933 will be approximately \$47,255.35. This is a reduction of \$14,121.23 from the expenditures of 1932 and is less than the budget appropriation for 1933 by \$3,431.32. The other financial statement presented to the Board of Regents showed the income and expenses from January 1, 1933, to October 31, 1933, and the estimated income and expenses from November 1, 1933, to December 31, 1933. The anticipated surplus for 1933, shown on this statement, was \$5,765.23. The Treasurer then asked the Executive Secretary, Mr. Loveland, to analyze the statements presented, which he did. Mr. Loveland pointed out to the Board of Regents that the income for 1933 had been greatly reduced for the following reasons:

- (1) Dues had been reduced approximately 25 per cent;

- (2) No elections to Fellowship or Associateship have taken place since the Annual Clinical Session at Montreal, whereas customarily there is a meeting of the Board of Regents in the middle of the year, when new elections take place and the fees and dues from such new members go into the year's income. This year, for

ABSTRACT OF MINUTES OF BOARD OF REGENTS

the sake of economy, the Board of Regents was not called together as many times as usual, and with the present meeting at the end of the year, most of the income arising from the new elections will go into next year's business;

(3) The change in the By-Laws requiring new candidates to be presented first for Associateship, has very greatly reduced the number of possible candidates for Fellowship. Whereas the 1931 income from Fellowship initiation fees amounted to \$18,365.00, the income from that source for the present year to date has amounted only to \$2,040.00;

(4) Financial stringencies of the times are responsible for a greater degree of delinquency in dues and in failure of subscribers to the Life Membership Fund to pay their annual subscriptions. For illustration, in 1931 income from subscriptions to the Life Membership Fund amounted to \$2,400.00, in 1930 to \$3,100.00, whereas the amount received to date this year was \$425.00;

(5) Income from bonds and income from interest on bank balances have been reduced due to the fact that we received no income on the balances in closed banks, that we received no income on balances in checking accounts since March 1933, and that \$4,000.00 of the Bonds of the City of Detroit defaulted in interest payments.

Strict economy has been practiced by all Officers of the College this year, and the prospect of finishing the year with a surplus appears to be gratifying indeed under the conditions outlined above.

By resolution, the report of the Treasurer and the Executive Secretary was approved.

REPORT OF THE COMMITTEE ON THE JOHN PHILLIPS MEMORIAL PRIZE

The Chairman of the Committee on the John Phillips Memorial Prize, Dr. David P. Barr, reported that the method of procedure in the selection of candidates for the 1934 award had been followed as previously, but that after a very careful survey by his Committee, there appeared to be no outstanding favorite among the candidates submitted, and that no exceedingly outstanding or meritorious piece of work had been completed during the past year by any of those under consideration. The Committee also felt that the Board of Regents might appropriately more definitely determine what the prize shall be in the future. The Committee presented the following recommendations:

- (1) That the Phillips Memorial Prize be not awarded this year;
- (2) While the directions to the Committee are specific as to the mode of conducting the competition for the prize, the Committee has no instructions as to what the prize shall be. It is recommended that the Board of Regents at their next meeting definitely establish what the policy shall be with regard to the exact nature and form of the award.

Thereafter the following resolutions were adopted:

RESOLVED, that the above recommendation (1) of the Committee on the John Phillips Memorial Prize be approved;

RESOLVED, that the present Committee on the John Phillips Memorial Prize formulate and present at the next meeting of the Board of Regents a recommendation with regard to the exact nature and form of the Phillips Memorial award.

REPORT OF THE EDITOR OF THE ANNALS OF INTERNAL MEDICINE

The Editor of the ANNALS OF INTERNAL MEDICINE, Dr. Maurice C. Pincoffs, reported that in accordance with authority granted by the Board of Regents he and the Executive Secretary, after making an extensive study of various printers, had selected the Lancaster Press, of Lancaster, Pa., beginning with the July 1933 number. This concern prints almost exclusively scientific journals and books. A considerable saving has been effected, and improved service has been obtained. The format of the journal has been changed, with the apparent approval of every one. A large number of manuscripts are received, there being an ample supply for some months to come. Approximately one in four of the manuscripts submitted is accepted. The work of the Editor's Office is carried on with the printers from two to three months in advance.

Discussion followed concerning the continuation of the publication of the present Editorial Council on the back cover of the Annals. This Council has not been an active one in recent years, and has probably been carried over from the time the late Dr. Warthin was Editor. General discussion disclosed that the present Committee on the ANNALS OF INTERNAL MEDICINE, consisting of three members, is a standing Committee having general responsibility for the Annals in questions relating to administration and publication. The thought was expressed that the present Committee might be modified to provide for five members, and that these five members need not necessarily be members of the Board of Regents. The present Editorial Council should be abolished and an active one appointed to function not only in relation to administration and publication, but also in relation to the publication of editorials, the selection of articles published and to share with the Editor the responsibility of rejecting manuscripts.

President Piersol summed up the discussion and expressed the consensus of opinion as being that the Editor of the Annals should be asked to get in touch with his Committee and at the next meeting of the Board of Regents to be ready to give recommendations for the modification of the present Committee, or some other plan for the appointment of an Editorial Council.

REPORT OF THE COMMITTEE ON PUBLIC RELATIONS

The Chairman of the Committee on Public Relations, Dr. Charles G. Jennings, presented reports on two cases involving contract practice and advertising. The Board of Regents directed the Committee to make a further and more complete study of the cases and report at the next meeting of the Board of Regents.

OLD AND NEW BUSINESS

President Piersol reported that on September 14, 1933, in accordance with provisions of the By-Laws, he had appointed the following members of the Board of Governors to serve until the next regular election:

Dr. Robert B. Kerr (Fellow), Manchester, Governor for New Hampshire;
Dr. Clarence L. Andrews (Fellow), Atlantic City, Governor for New Jersey.

These appointments were occasioned by the death of Dr. Edward O. Otis, Governor for New Hampshire, and by the death of Dr. W. Blair Stewart, Governor for New Jersey. Dr. Ernest B. Bradley, Vice Chairman of the Board of Governors, now succeeds to the Chairmanship of the Board of Governors and becomes ex officio a member of the Board of Regents, until the next regular election.

On behalf of the Nominating Committee, the Executive Secretary asked the wishes of the Board of Regents regarding the nomination of a Governor of the Col-

ABSTRACT OF MINUTES OF BOARD OF REGENTS

lege for Puerto Rico. The College has a few members in Puerto Rico, and there has been a recommendation that an official Governor should be elected to facilitate the presentation of candidates from that Island. The Board concurred in the opinion that the Nominating Committee should nominate a Governor for Puerto Rico.

The Executive Secretary reported that the resignations of Dr. James J. Gable (Associate), Norman, Okla., and Dr. Everett E. Watson (Associate), Salem, Va., held over from the last meeting of the Board of Regents, had been withdrawn and their active memberships reestablished.

The Executive Secretary then reported that Dr. Ray G. Barrick (Associate), Joliet, Ill., and Dr. James E. Harvey (Associate), Pasadena, Calif., had been dropped from the roll because of failure to take up their election in the prescribed period of one year.

The Executive Secretary was authorized to dispense with the services of an official medical reporter for the general scientific sessions at the next Clinical Session.

The following resolution was adopted:

RESOLVED, that the matter of the adoption of a Life Membership Certificate be referred to a Committee of three, who shall report to the Board of Regents at their next meeting.

Dr. Walter L. Bierring reported that the Council on Medical Education and Hospitals of the American Medical Association had been requested to investigate the entire subject of specialization and make recommendations, looking to the establishment of proper qualifications of physicians who shall engage in special practice and that the report of the Council and its recommendations be submitted to the House of Delegates as soon as practicable. In compliance with these instructions, after a two year study, the Council had determined that it seemed desirable to bring together, for mutual discussion, some of those who are interested in various phases of this problem, and a preliminary meeting had been held at Milwaukee on Sunday, June 11, at the Hotel Wisconsin. The conference was arranged jointly by some of the special examining boards, by the National Examining Board and by the Council. Dr. William D. Cutter, of the Council on Medical Education and Hospitals of the American Medical Association, invited the American College of Physicians to send a representative to that meeting, and President Piersol had asked Dr. Bierring to represent us, although Dr. Bierring was officially there on behalf of the Federation of State Licensing Boards. Among other organizations represented were the American Association of Medical Colleges, the Council on Medical Education and Hospitals of the American Medical Association, the National Examining Board, the American Board of Ophthalmology, the American Board of Pediatrics, the Board for Orthopedics, the Board for Obstetrics and Gynecology, the Board for Proctology and the Board for Psychiatry. Dr. Louis Wilson, of Rochester, Minn., presided. Dr. Paul Titus, of Pittsburgh, acted as Secretary, and Dr. W. P. Wherry, of Omaha, was in charge of arrangements. The meeting resulted in general discussion of a means for the certification and licensure of specialists in the various fields of medicine. Suggestions for a constitution of an "Advisory Council on Medical Specialists" were presented and further meetings scheduled for future development of this Advisory Council.

In the general discussion that followed, the consensus of opinion was that the American College of Physicians should take immediate action looking toward its participation in the certification of internists and others engaged in affiliated specialties. The College is the natural body to function in this field, and the Board of Regents might initiate written examinations, for which machinery is already set up

in the By-Laws for the admission of candidates to Fellowship, and might further initiate additional examinations for certification of physicians as specialists in internal medicine and affiliated specialties. On motion seconded and regularly carried, it was

RESOLVED, that the Chair appoint a Committee of three to make a complete and thorough study of this situation and report back at the next meeting of the Board of Regents.

The Secretary-General, Dr. William Gerry Morgan, read a communication from Surgeon General Robert U. Patterson, of the U. S. Army, concerning the support by various medical organizations of the project for the building of a new library for the Medical Department of the Army, in connection with the Walter Reed Medical Center. The recommendation of the Board of Regents was that this is a worthy project and should be encouraged, and suggested that the Secretary-General write to the proper officials advocating the building of the library but refraining from suggesting the source from which funds therefor should be taken, because this is not in the domain of the College.

Secretary-General Morgan then read a communication from Dr. William H. Walsh (Fellow), Chicago, presenting a proposed plan for a Council on Professional Service and Administrative Practice. The proposal provided that the Council should be specifically directed to the problems involving various economic phases of practice, methods and procedures for the certification of specialists, standards for the practical training of technicians, dietitians, clinical record librarians in hospitals, etc.

On behalf of the Chairman of the Committee on Clinics, Dr. Arthur R. Elliott, the Executive Secretary presented for the consideration of the Board the matter of an official scientific exhibit at future annual meetings. Dr. Elliott had pointed out that it is probably desirable to forego such an exhibit this year but recommended that the idea of a systematic scientific exhibit in the future should be considered by the Board of Regents as one of the principal activities of the College.

President Piersol at this point presented an invitation from Philadelphia to the American College of Physicians to meet in that City during 1935.

Adjournment.

Attest: E. R. LOVELAND,
Executive Secretary.

NATIONAL PNEUMONIA SERA



The Research Laboratories of The National Drug Company have made close studies of producing and refining Anti-Pneumococcic Sera. A method of immunizing horses and a process of concentrating and refining pneumonia sera have been devised enabling us to offer super-refined and extra-concentrated sera approximating six to ten times the potency of the unrefined sera, with a corresponding decrease of inert solids and proteins.

The chill producing substances have been largely removed.

The Refined Pneumonia Sera contain all the specific antibodies, agglutinins, or other antitoxic or antibacterial substances contained in the whole sera; are crystal clear and of the same viscosity as normal serum; the pH is adjusted with meticulous care.

Doses of 10 to 20 cc., repeated every six to eight hours, or as advisable, may be given until a favorable response is secured. The patients' sputum should be typed early and if Type I, II, or III pneumococci are present the serum should be continued.

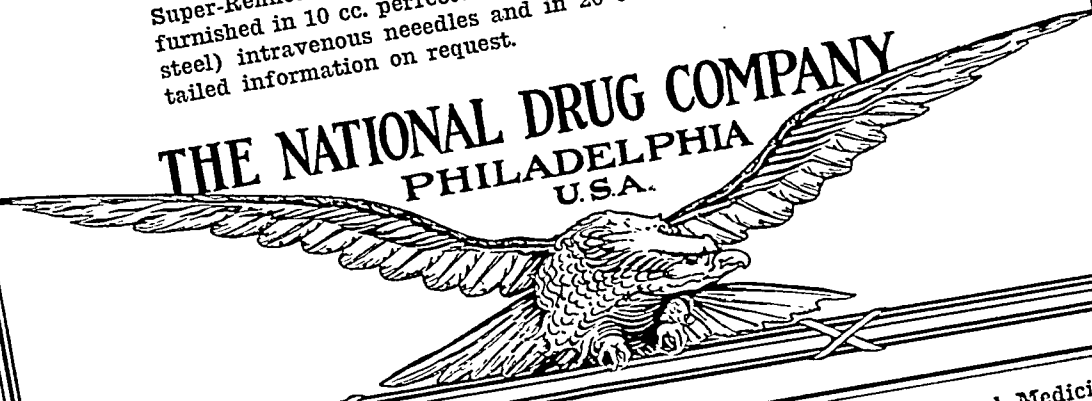
Pneumonia Polyvalent Serum for Types I, II, or III pneumonia.

Pneumonia Bivalent Serum for Types I and II pneumonia.

Pneumonia Monovalent Serum for Type I pneumonia.

Super-Refined and Extra-Concentrated Pneumonia Sera are furnished in 10 cc. perfected syringes with chromium (rustless steel) intravenous needles and in 20 cc. ampoule-vials. Detailed information on request.

THE NATIONAL DRUG COMPANY
PHILADELPHIA
U.S.A.



Send detailed information on Refined Pneumonia Sera per Annals of Internal Medicine.

Name

City

State

Date

Consultation and Advisory Service

HOSPITAL PLANNING
ORGANIZATION
MANAGEMENT
AND EQUIPMENT

GROUP HOSPITALIZATION

SURVEYS CONDUCTED FOR
INDIVIDUAL HOSPITALS OR
ENTIRE COMMUNITIES

Office of

WILLIAM HENRY WALSH, M.D.
612 North Michigan Avenue
CHICAGO

The WYATT CLINIC

for

Chronic Arthritis

at

TUCSON, ARIZONA

LaMOTTE SERVICE

IMPROVED KLINE ANTIGEN
FOR
PRECIPITATION TESTS
FOR SYPHILIS

This improved Antigen is now being produced under an exclusive arrangement with the Mount Sinai Hospital of Cleveland, in whose laboratory the method of preparation was developed. Each lot of antigen is tested in this same laboratory and only approved Standardized Antigen is released by us for distribution.

Far superior in the sero diagnosis of syphilis.

May be used for tests on spinal fluid. Antigen solution has excellent keeping qualities.

Sensitive at low temperatures.

Prices and full information on the antigen and the new simplified compact outfits for these tests sent on request.

Your LaMotte Blood Chemistry Handbook * illustrates and describes many simple, accurate testing outfits developed by LaMotte Research Department in cooperation with recognized specialists.

* If you do not have one, write today for a complimentary copy.

AMOTTE CHEMICAL PRODUCTS CO.
18 Light St. Baltimore, Md.

*? Will your diabetics
have 1065 satisfactory
meals in 1934 ?*

** **

They should and can.

May we assist you, Doctor ?

** **

**FOODS FOR LOW-CARBOHYDRATE
AND MODERATE PROTEIN DIETS**

** **

*Literature and samples
on request*

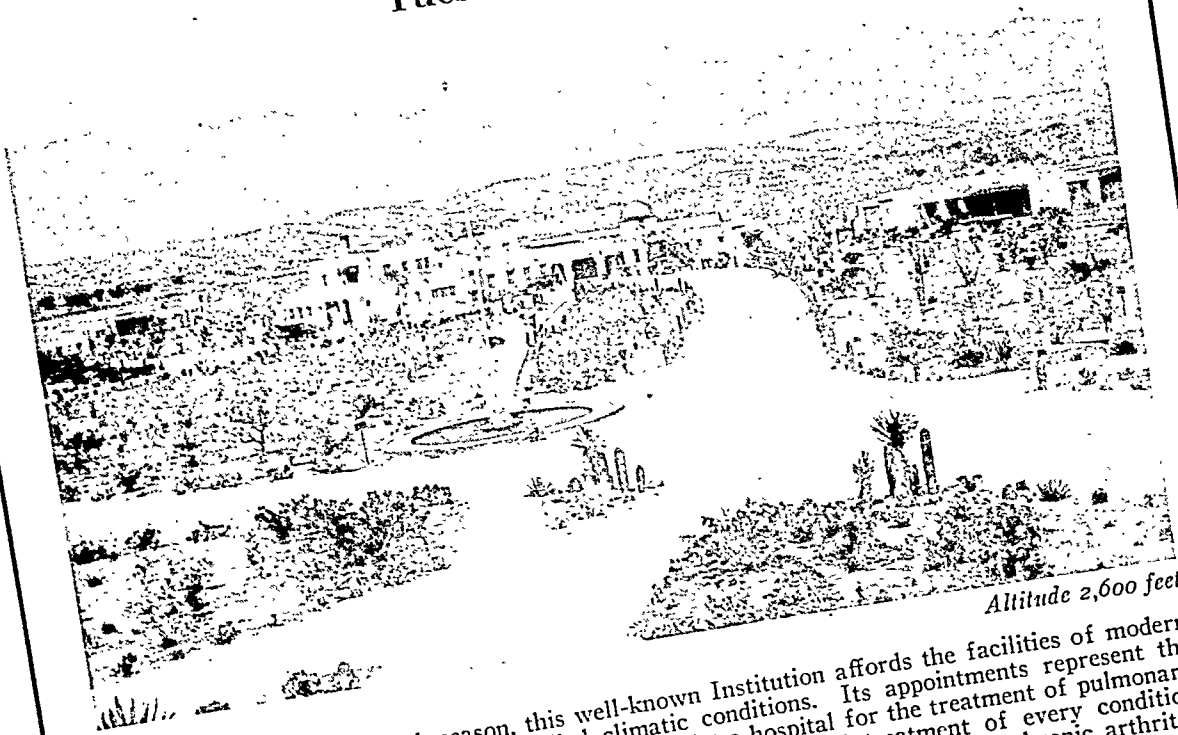
CURDOLAC FOOD COMPANY

Box 299

Waukesha, Wis.

The Desert Sanatorium and Institute of Research

Tucson, Arizona



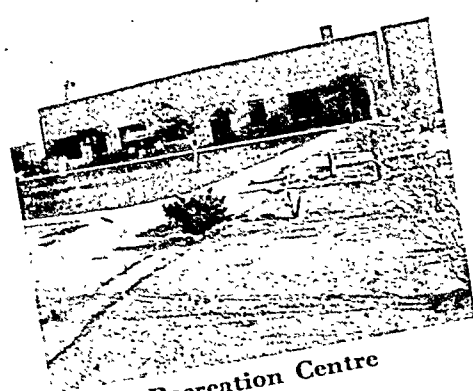
Altitude 2,600 feet

Entering upon its eighth season, this well-known Institution affords the facilities of modern diagnosis and treatment under unexcelled climatic conditions. Its appointments represent the acme of attractiveness, comfort and convenience. Not a hospital for the treatment of pulmonary tuberculosis, it aims at the utmost perfection of diagnosis and treatment of every condition that may be benefited by a warm, dry, sunny climate of desert type, such as chronic arthritis, sinusitis, nontuberculous pulmonary and upper respiratory complaints, arterial hypertension, cardiorenal insufficiency, etc.

W. PAUL HOLBROOK, M.D., *Physician-in-Chief*
VIVIAN TAPPAN, M.D., *In Charge of Pediatrics*

ALLEN K. KRAUSE, M.D., *Director*

MAX PINNER, M.D., *Director of Laboratories*
CHARLES W. MILLS, M.D., *In Charge of Visiting Staff*



Recreation Centre



Out-Patient Clinic

For RATES AND OTHER INFORMATION
Address *Secretary, Desert Sanatorium*
Tucson, Arizona

WRITE FOR BOOKLET

Please Mention this Journal when writing to Advertisers

LEA & FEBIGER BOOKS ON DIET

NEW (5th) EDITION

JUST READY

A DIABETIC MANUAL

For the Mutual Use of Doctor and Patient

By **ELLIOTT P. JOSLIN, M.D.**

Clinical Professor of Medicine, Harvard Medical School; Medical Director, George F. Baker Clinic for Chronic Disease at the New England Deaconess Hospital; Consulting Physician, Boston City Hospital, Boston, Mass.

12mo., 224 pages, illustrated with 49 engravings and a colored plate. Cloth, \$2.00, net

JOSLIN'S Diabetic Manual should be in the hands of every diabetic patient. Here are the full instructions for carrying out home treatment under the care of the general practitioner. The book answers all of the essential questions concerning food values, diet calculations, danger signs and insulin. This new edition covers every advance concerning the use of insulin and the dietary treatment. It instructs the patient how to be his own nurse and chemist, but not his own physician. This book should be the first prescription for the diabetic patient.

NEW WORK

JUST READY

METABOLIC DISEASES AND THEIR TREATMENT

By **DR. ERICH GRAFE**

Professor of Medicine and Director of the Clinic of Medicine and Neurology at the University of Würzburg, Germany

Translated by Margaret Galt Boise, Under the Supervision of

EUGENE F. Du BOIS, M.D. and HENRY B. RICHARDSON, M.D.

Medical Director, Russell Sage Institute of Pathology; Professor of Medicine, Cornell University Medical College, New York

Associate Professor of Medicine, Cornell University Medical College, New York

Octavo, 551 pages, illustrated with 37 engravings. Cloth, \$6.50, net

THIS work by an authority of world-wide reputation deals chiefly with treatment, and includes the important discoveries of the last few years. After considering general nutritional disorders, the chief metabolic diseases are covered in detail with particular attention to Obesity, Habitual Undernutrition (Magersucht), Diabetes Mellitus, Diabetes Insipidus, Gout, Alcaptonuria, Cystinuria and Aminuria. The appendix covers briefly other conditions not properly classified as metabolic diseases but usually associated with them.

NEW WORK

JUST READY

DIETETICS FOR THE CLINICIAN

By **MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P.**

Associate in Medicine at the New York Post-Graduate Medical School, Columbia University, New York

IN COLLABORATION WITH

WITH A FOREWORD BY

RUTH LOTHROP GALLUP

HERMAN O. MOSENTHAL, A.B., M.D.

Dietitian
Los Angeles

Director of Medicine at the New York Post-Graduate Medical School, Columbia University,
New York

Octavo, 666 pages. Cloth, \$6.50, net

THIS is a work on dietary management which is not only readily understandable but from which practice can be immediately instituted. It devotes 400 pages to the dietetic indications of over 100 common diseases, furnishes sample menus for three days in each case. This unique feature makes the book of real practical value not only to every general practitioner but to the specialist as well. The surgeon, pediatrician, otolaryngologist, dentist, endocrinologist, urologist and the specialist in tuberculosis, allergy, and diabetes is provided with material prepared in collaboration with experts in his field.

LEA & FEBIGER

Please send me books checked:

- ☐ Joslin's Diabetic Manual - \$2.00
☐ Grafe on Metabolic Diseases 6.50



- ☐ Bridges' Dietetics - - \$6.50
☐ New Catalogue

600 Washington Square
PHILADELPHIA, PA.

Name.....

(A. of I. M. 2-34)

Address.....

ACCEPTANCE

British and
American Reviewers
Laud—

Barclay's THE DIGESTIVE TRACT

Quarto—395 pages—275 illustrations—\$12.00

Excerpts from Reviews—

"A magnificent volume of 395 pages, with 275 figures. The book is in fact a comprehensive monograph which is probably destined to become a classic in its field. It is the first book in English, if not in any language, to bring together the new information which X-rays have thrown on anatomy and physiology, and it is also far and away the most complete work which has appeared on this branch of pathological diagnosis."

—*Cambridge Review*

"Of special interest is the recent work on the physiology of the gastric mucous membrane. In addition to the main sections on Technique, Anatomy, Physiology and Pathology, there are valuable appendices on the organization and equipment of an X-ray Department and on the radiation risks run by the radiologist. The numerous illustrations are almost without exception admirable, and the reproductions of actual radiograms form in themselves an atlas of gastro-intestinal radiography."

—*Oxford Magazine*

"This book with its well chosen and executed cuts, systematic arrangement of the subject matter and completeness of its information on this subject, is enthusiastically recommended. The writer is attracted by the clear, and at the same time entertaining style found throughout this book."

—ARTHUR E. PERLEY in *Radiological Review*

"One of the many excellent chapters in Dr. Barclay's book is devoted to a study of the normal mechanism of swallowing, the author himself having made many fundamental observations along this line. He calls attention to the extraordinary fact that so little research seems to have been carried out on the mechanism of swallowing, an act which is of such supreme importance to a person's well-being, and that gravity which has always played such an important part in any discussion of the act of swallowing is in reality a negligible quality. He has found that the process of swallowing as seen roentgenologically consists in three fundamental changes, etc."

—excerpt from 3½ page editorial on Dr.
Barclay's book in the *American Journal*
of *Rocntgenology and Radium Therapy*

THE MACMILLAN COMPANY—60 FIFTH AVENUE—NEW YORK

THE DIGESTIVE TRACT

A Radiological Study of Its Anatomy,
Physiology and Pathology. By ALFRED
BARCLAY, M.D. Lecturer in Medical
Radiology, University of Cambridge.

Gentlemen—

Send and charge Barclay's
THE DIGESTIVE TRACT. \$12.00

Name

Address

CityState

Please Mention this Journal when writing to Advertisers

COUNCIL ACCEPTED

THEOCALCIN

(theobromine-calcium salicylate)

A well tolerated diuretic and myocardial stimulant indicated in cardiovascular disease with, or without, renal insufficiency. . . .

7½ grain Tablets and Powder.

DOSE: 7½ to 22½ grains t. i. d. with or directly after meals.

Literature and samples upon request.

BILHUBER-KNOLL CORP.

154 OGDEN AVENUE, - JERSEY CITY, N. J.



Eighteenth Annual Clinical Session

OF THE

**AMERICAN COLLEGE
of PHYSICIANS**

CHICAGO, ILL.

April 16-20, 1934



Headquarters: PALMER HOUSE

JAMES B. HERRICK, M.D., Chicago,
General Chairman

GEORGE MORRIS PIERSOL, M.D.,
Philadelphia, *President*

PROFESSIONAL PROTECTION



RIGHT THRU THE DEPRESSION

1929—Surplus to
Contract Holders \$1,131,173

1933—Surplus to
Contract Holders \$1,209,036

"THE LITTLE GIANT"

THE

MEDICAL PROTECTIVE COMPANY

OF FORT WAYNE, INDIANA

WHEATON, ILLINOIS

Please Mention this Journal when writing to Advertisers

Devitt's Camp, Inc.

ALLENWOOD
PENNSYLVANIA

(Tuberculosis)

*On beautiful White Deer Mountain, 20 miles southeast
of Williamsport, Pa.*

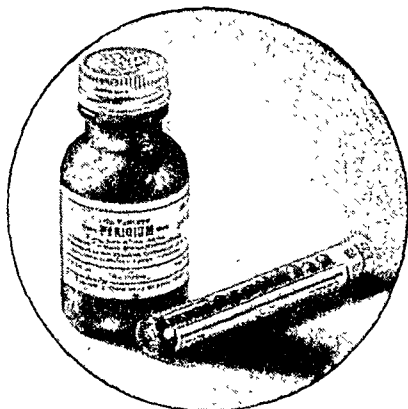
DEVITT'S CAMP was started in April of 1912 to take care of three men who would not leave their families. There was no intention of making it a tuberculosis sanatorium. The first patients slept in a barn. Since that time the Camp has grown until it comprises bed capacity for 115 patients, and has a staff of three full time physicians and thirteen nurses. It is fully equipped to take care of persons suffering from pulmonary tuberculosis. It has grown in value from a barn to a value of \$348,000. We have endeavored to render the best service irrespective of cost. Special effort has always been made to make the surroundings cozy and homelike. We have always felt that the best asset of the Camp has been the spirit of cooperation which is maintained between the staff and the patients. Forty per cent of the patients are receiving artificial pneumothorax, and other operative procedures such as phrenicectomy, Jacobaeus operation, and thoracoplasty are taken care of in nearby surgical centers by skilled chest surgeons.

Devitt's Camp would be very glad to take care of your patients for you. A full report is sent to each family physician of every examination and x-ray. The rates are moderate—\$23.00 and \$30.00 per week which includes everything except personal laundry and necessary x-ray plates which are charged for at cost. We will be glad to send you a booklet if you are at all interested.

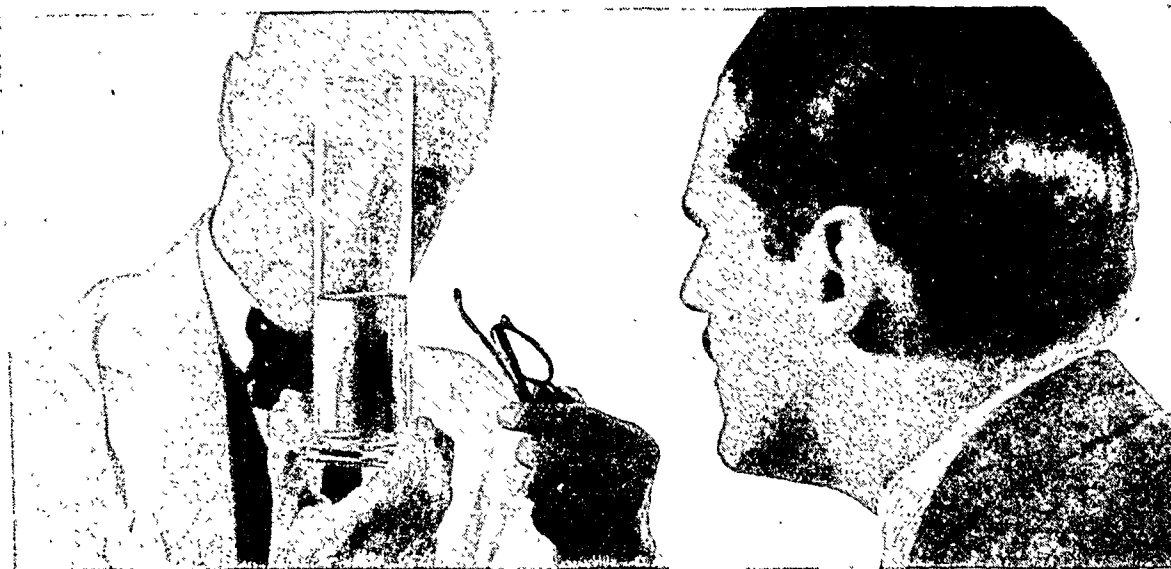
ROSS K. CHILDERHOSE, M.D.
JOHN S. PACKARD, M.D.
Associate Physicians

WILLIAM DEVITT, M.D.
*Superintendent and
Physician in Charge*

RELIEF OF



**FREQUENCY
TENESMUS
LUMBAR PAINS**



• the result of PYRIDIUM orally administered in urinary infections

The oral administration of Pyridium shortens the period of treatment in the majority of cases of cystitis—pyelitis—urethritis. Pyridium also affords early relief of the distressing symptoms usually associated with urinary infections.

LITERATURE ON REQUEST

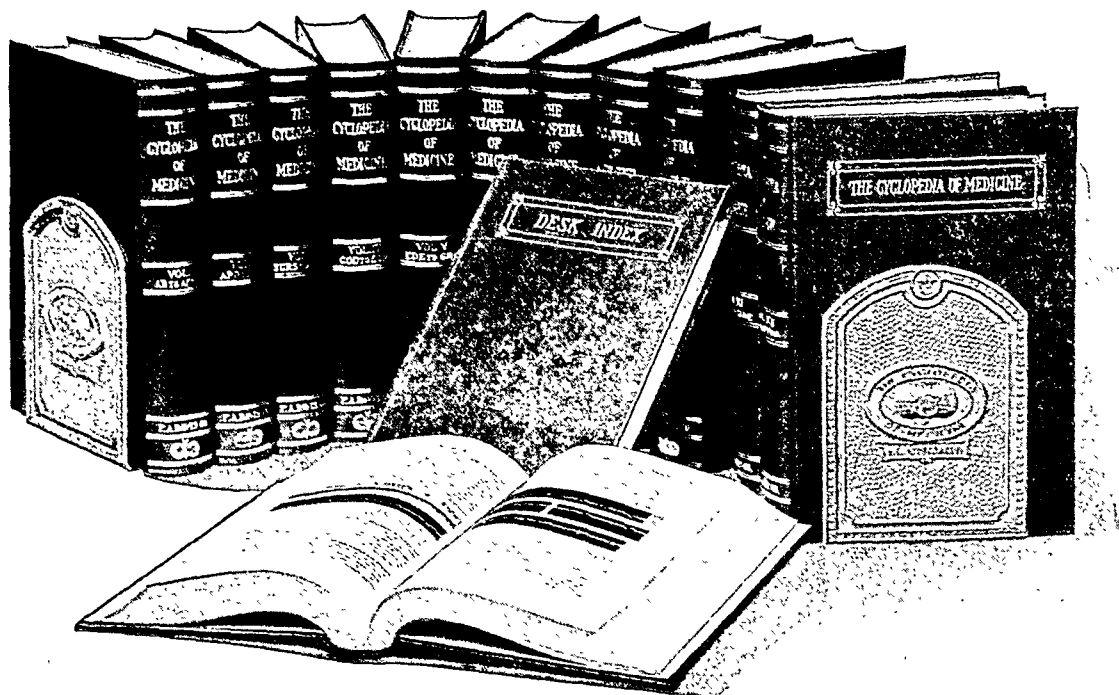


MERCK & CO. INC.

Manufacturing Chemists

Rahway, N. J.

700 PHYSICIANS ^A_N^D SURGEONS AT YOUR COMMAND



THE CYCLOPEDIA OF MEDICINE

GEORGE MORRIS PIERSOL, B.S., M.D.

EDITOR-IN-CHIEF

EDWARD L. BORTZ, A.B., M.D.

ASSISTANT EDITOR

CHIEF ASSOCIATE EDITORS:

W. WAYNE BABCOCK, A.M., M.D.

P. BROOKE BLAND, M.D.

CONRAD BERENS, M.D.

FRANCIS L. LEDERER, B.S., M.D.

A. GRAEME MITCHELL, M.D.

* 20 ASSOCIATE EDITORS AND 700 CONTRIBUTORS

The contributors have been selected from the faculties of 69 leading medical schools in the United States and Canada, 18 in England, France, Germany, Italy, Russia, Brazil and eight other foreign countries. Many are the recognized authorities in world famous clinics, research institutes, and other medical foundations. All have established reputations for outstanding work in their respective fields.

"This is a work of outstanding importance. It is conceived along broad lines, is remarkably comprehensive, and thoroughly up to date. We have in these volumes, in readily accessible form, the marrow of Medical knowledge, an epitome of many medical libraries, a complete and authoritative exposition of the science and art of medicine. We commend the Cyclopaedia without hesitation."—*Canadian Medical Association Journal*.

"A constantly modern library of monographs on medicine, surgery and the specialties, published in Cyclopedic form both for the convenience and economy of the profession."

* SUPPLEMENTED ANNUALLY

F. A. DAVIS COMPANY

1914-16 CHERRY STREET
PHILADELPHIA

Please send me complete descriptive material about *The Cyclopaedia of Medicine*.

Name

Address

Please Mention this Journal when writing to Advertisers

Double Assay

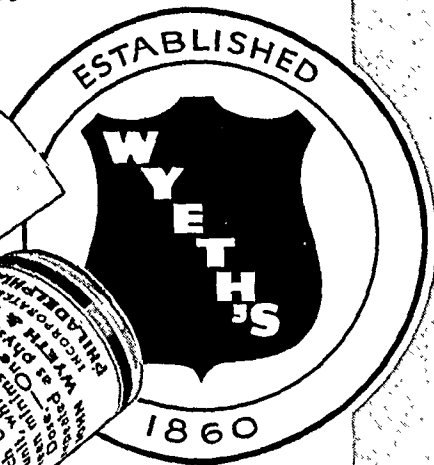
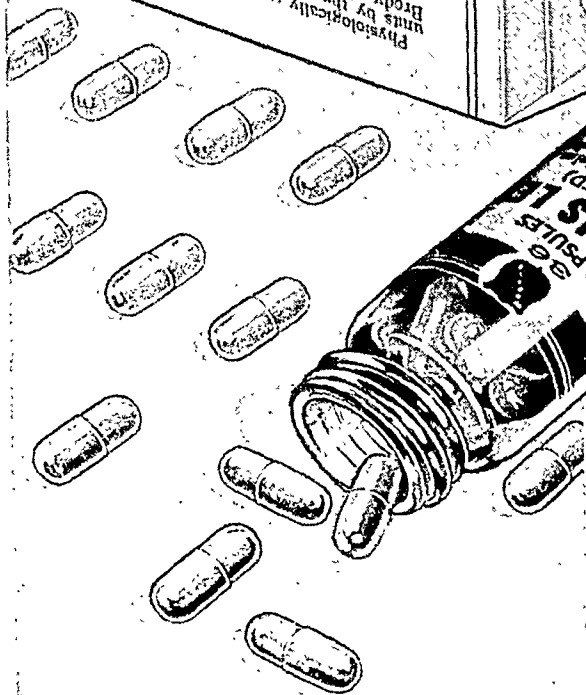
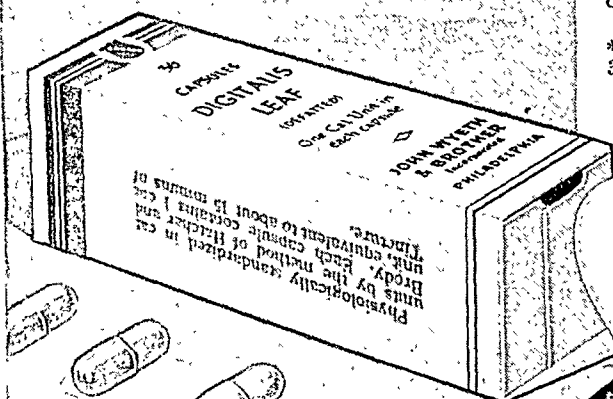
Both the U. S. P. frog method and the cat unit method of Hatcher and Brody are employed in testing every batch of Wyeth's Capsules Digitalis Leaf (Defatted).

When the activity with frogs and cats is fairly parallel, the absorption may be considered as normal; whilst wide divergence is usually associated with abnormality in the clinical response. It would therefore be safest to assay the preparations by both methods, and to reject those that do not give concordant results. Those which agree should be adjusted to the U. S. P. standard.*

Wyeth's Capsules Digitalis Leaf (Defatted) are supplied in vials of 36 and 100 distinctive green capsules.

If you have not already had an opportunity to submit Wyeth's Digitalis to test, we will be glad to send you a package with our compliments.

*A Manual of Pharmacology, Sollman, 3d Ed., p. 530.



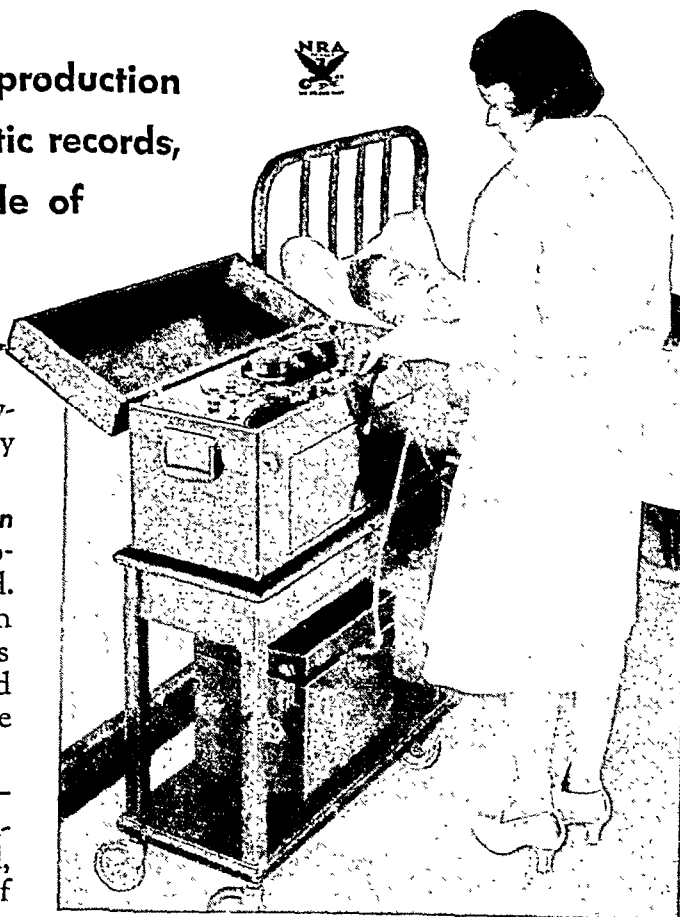
*Control the Integrity
of Your Prescriptions
by Specifying Wyeth's
Pharmaceuticals*

**JOHN WYETH &
BROTHER, Inc.**

Philadelphia, Pa. and Walkerville, Ont.

General Electric ELECTROCARDIOGRAPH

Insures consistent production
of reliable diagnostic records,
due to the principle of
tube amplification



No Overshooting—this annoying factor completely eliminated.

No Compensation for Skin Current Necessary—no protective resistance required. Thus another complication in the older procedure is removed, saving time and further insuring an accurate record.

High Speed of Deflection—which characterizes this instrument, cannot be affected, regardless of the amount of body resistance.

Constant Speed of Deflection under all conditions of operation, as the galvanometer is permanently set at the factory and sealed in oil. No string to adjust.

Simplicity of Operation makes it possible for the physician or his office assistant to learn how to operate it in an hour, to produce tracings equal

in diagnostic value to those formerly obtained with complicated instruments which required skill and years of experience to master.

Send for complete description of the new model G-E Electrocardiograph, with its timing device, automatic lead marker, time and amplitude measuring lines superimposed on record, and other features.

GENERAL ELECTRIC  **X-RAY CORPORATION**

2012 Jackson Blvd.

Branches in Principal Cities

Chicago, Illinois

BIVALENT Antipneumococcic Serum Lederle TYPES I AND II

REFINED AND CONCENTRATED

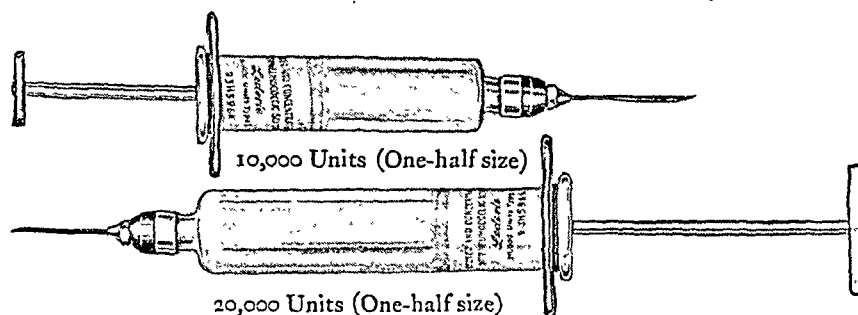
has been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

When it is considered that more than 50 per cent of all pneumonia cases between the ages of five and fifty years are either Type I or Type II, the importance of a bivalent antipneumococcic serum effective in these types will be appreciated. Between the ages of twenty and forty years the incidence of these two types is even greater.

The Department of Health of the City of New York in their Quarterly Bulletin, Vol. 1, p. 30, states:

"Bivalent type I and II antiserum may be used in the treatment of lobar pneumonia in adults before the infecting type is determined, as 40 to 50 per cent of the cases in this locality are caused by types I and II."

From the standpoint of lower mortality as well as economy of treatment, Bivalent Antipneumococcic Serum (Lederle) deserves your consideration.



Syringe containing 10,000 units each of Type I and Type II. \$ 7.00
Syringe containing 20,000 units each of Type I and Type II. 12.00

FOR RAPID TYPE DIAGNOSIS

Monovalent typing sera from rabbits, adapted for rapid typing by the Neufeld reaction as described by Sabin,* are available.

One Package (5 tubes) Type I \$0.50

One Package (5 tubes) Type II. 0.50

*A. B. Sabin, J. A. M. A., May 20, 1933.

Literature upon Request

LEDERLE LABORATORIES INC.

511 FIFTH AVENUE, NEW YORK

TWO FUNDAMENTALS IN THE TREATMENT OF DIABETES . . .

Insulin ... *Diet*

As we know, the diet will vary with the needs of the individual patient.

But the Insulin should always be a constant, unvarying, dependable therapeutic agent.

When you use Insulin-Stearns, you know that it is prepared under such exacting conditions of laboratory manufacture that it is:

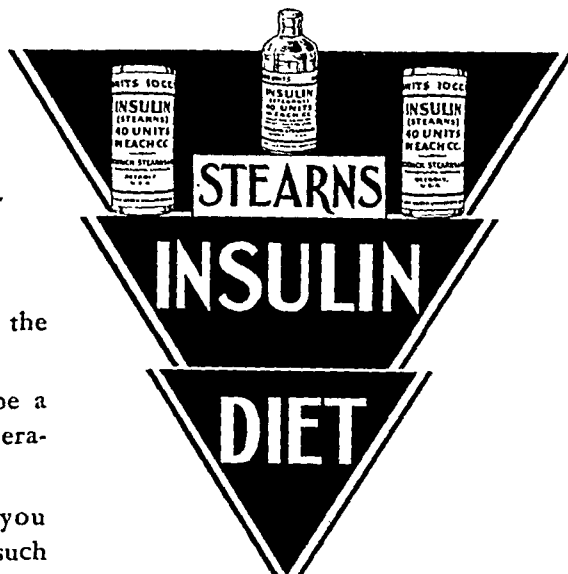
Biologically exact in potency

Remarkably clear

Notably free from sting

at point of injection

We take the utmost pride in the efficiency of our Insulin department with its modern equipment and its scientific



personnel, and we are only too glad to demonstrate the step-by-step process of manufacture to interested physician visitors.

Let us send you complete literature describing Insulin-Stearns—how it is made, how it is supplied and recommended for use in actual practice. The facilities of Stearns Insulin Research Department are always at your service.

FREDERICK STEARNS & COMPANY
DETROIT, MICHIGAN, U. S. A.

FREDERICK STEARNS & COMPANY
Detroit, Michigan

A.I.M. 1

Gentlemen: I will be glad to have complete literature describing Insulin-Stearns.

Doctor.....

Address.....

City.....*State*.....



a new anti-anemic preparation
with a tang and zest all its own

AUTOLYZED LIVER *Concentrate*

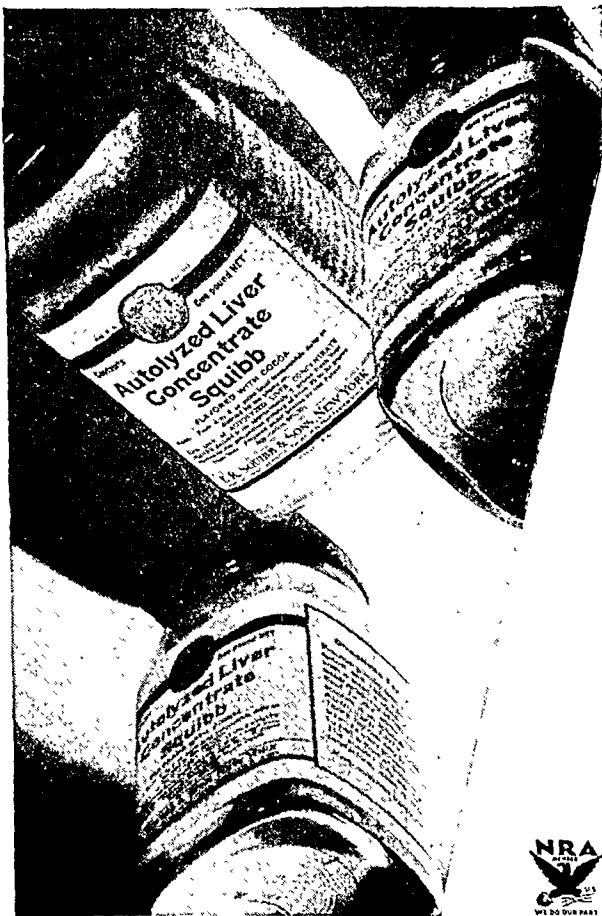
SQUIBB

AUTOLYZED LIVER CONCENTRATE SQUIBB provides all the blood regenerative properties of whole liver and yet its taste is far removed from liver itself. It has a tang and zest all its own when mixed with sweet butter and spread on bread. It can be taken also in warm bouillon or dissolved in milk.

Autolyzed Liver Concentrate is not like any other liver preparation. It is not an extract. It is prepared from whole liver, *autolyzed*, powdered and flavored with cocoa. Its use is promptly followed by a noticeable increase in red blood cells and hemoglobin and a noteworthy improvement in appetite, weight and strength.

Although primarily designed for use in the treatment of pernicious anemia, it deserves study as a diet supplement of convalescents particularly after operations where the blood loss has been severe or in the anemias of pregnancies. In addition to its anti-anemic potency it has almost twice the Vitamin B and G activity of dried yeast.

Autolyzed Liver Concentrate Squibb is economical to use—costing as little



Manufactured under license to use U. S. Patent Application Serial No. 620,301. Marketed in ½ and 1-lb. bottles. Council accepted



as 7 cents a day for the first year's treatment of an uncomplicated case of pernicious anemia. One gram of the concentrate is equal in anti-anemic potency to from 20 to 30 grams of fresh liver.

E. R. SQUIBB & SONS, NEW YORK
MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858.



ULYSSES S. GRANT—18th PRESIDENT OF THE UNITED STATES

*Since Grant was President
there has been but One Genuine*

Maltine
Reg. U. S. Pat. Off.

IN 1875, during the administration of President Grant, The Maltine Company was established for the purpose of developing malt preparations for medicinal use. Since the introduction of Maltine With Cod Liver Oil, many important developments in this field have been contributed by this company.

The high regard in which Maltine products are held by the medical fraternity has resulted in the unintentional use of the name "MALTINE" in its generic sense, with the result that some druggists have offered inferior preparations as "Maltine-type" or "the same as Maltine." As the name Maltine is the exclusive and registered property of The Maltine Company and can be used only on products manufactured by this company, patients can be protected against substitution by

prescription designating by name the particular Maltine product indicated.

One of the Maltine products imitated is Maltine With Cod Liver Oil. This "Council Accepted" product is the only one of its type in which the vitamins A, B, D and G content is *guaranteed*. It is composed of 70% Maltine, a concentrated fluid extract of the nourishing elements of malted barley, wheat and oats (excellent sources of vitamins B and G), and 30% vitamin-tested cod liver oil of high potency in vitamins A and D. Administered with orange or tomato juice, the fifth vitamin, C, is added. Maltine With Cod Liver Oil is standardized. Biological report sent to physicians on request. Address The Maltine Company, 30 Vesey Street, New York, N. Y.

This Trade-mark Identifies the Only Genuine

Maltine
Reg. U. S. Pat. Off.

Member NRA
We do our part

WITH COD LIVER OIL—Introduced in 1875



Calcium Deficiencies IN TETANY

"WHEN all the facts of tetany are arrayed it is impossible to escape the impression that there is a fundamental relation between the various types," is the opinion of Peters and Van Slyke.¹

The disorder may take such forms as the spasmophilia of infancy, the tetany of pregnancy, the convulsions of uremia, postoperative tetany, parathyroid tetany, and that associated with osteomalacia.

Cantarow² finds that when serum calcium falls below 7 mg. per 100 c.c. symptoms of tetany are manifest.

Alfred Hess notes that tetany occurs "frequently, in fact generally, in a latent form."³ In view of this the physician must be on guard against tetany in those cases where there is likely to be a drain on the calcium stores, particularly during growth and in pregnancy and lactation. Considering that the average diet is probably lower in calcium than in any other chemical

element, the problem of increasing calcium intake through ordinary foods is difficult. Calcium salts, moreover, are not usually relished by the patient.

A larger intake of calcium alone is not effective, however, unless the body is able to utilize the added minerals. Moreover, tetany is marked by elevations of serum phosphorus, according to Collip.⁴ Thus the problem arises not only of increasing calcium concentration but also of maintaining the proper ratio between calcium and phosphorus. "Vitamin D, as is well known, has remarkable power to regulate calcium and phosphorus metabolism," McCollum observes.⁵

Alfred Hess declares increased calcium intake together with viosterol to be the treatment of choice in tetany.³ He adds the significant comment that in tetany viosterol is characterized by its rapid action, whereas cod liver oil, in infantile tetany at least, appears to act upon the concomitant ricketic condition rather than upon the tetany.

MEAD'S CEREAL*

Enriched with mineral and
vitamin containing foods

SUPPLIES Calcium

Containing 0.22 Gm. Ca and 0.17 Gm. P per ounce, this delicious cereal is richer in these minerals than most principal foodstuffs. Two ounces supplies as much calcium as 12 ounces of fluid milk and thus obviates the need for excessive quantities of liquid in the diet. It also makes good the iron and vitamin B deficiencies of milk.

MEAD'S VIOSTEROL

IN OIL 250 D

UTILIZES Calcium

Alfred Hess says of viosterol: "One of the distinctive characteristics of this remarkable substance is that it raises the level of either inorganic phosphorus or of calcium, depending on which is in low concentration in the blood or tissues."³ Uniformly potent, accurately assayed, Mead's Viosterol can be depended upon for good results in tetany.

¹⁻⁵ Bibliography on request.

MEAD JOHNSON & CO., Evansville, Ind., *Pioneers in Vitamin Research*

Please enclose professional card when requesting samples of Mead Johnson products to cooperate in preventing their reaching unauthorized persons

* Now also supplied in pre-cooked form, as PABLUM. Dried, ready to serve by simply stirring (with a fork) with water or milk, hot or cold. Completely prepared in the cereal bowl in a few moments.

Please Mention this Journal when writing to Advertisers

added the concept of constitutional weakness (*asthenia congenita*) by which he meant to include psychic and emotional instability as well as the mechanical defects. Dubois claims that 90 per cent of all dyspeptics are psychoneurotics. The work of Cannon and others has shown that hormonal influences are associated with these psychic factors. It is questionable indeed whether nervous dyspepsia ever occurs as a purely functional state in the sense that Leube conceived. The complexity of the whole matter is due to the mutable and bizarre manifestations of personality variations. Certain definite patterns, however, are presented just as in other psychoneuroses. Thus either aerophagia, peristaltic unrest, rumination, anorexia, or persistent vomiting may be the outstanding symptom in an individual case. It is these latter two complaints that are the characteristic feature of the pernicious type of nervous dyspepsia.

We find a variable number of factors, any one of which may dominate the situation in nervous dyspepsia. I believe that some sort of schema is desirable in order to facilitate the recognition of the different types met with in practice. The following classification has served me satisfactorily:

1. Cases of purely psychic origin which remain without extension to the periphery, i.e., the pure hypochondriacal type.
2. Cases, neurogenous in origin, in which a local defect resulting from toxic substances, fatigue, infection, trauma or autogenesis is attended by centripetal extension.
3. Cases of psychic causation with centrifugal extension and centripetal repercussion.
4. The psychoses with delusions in reference to the alimentary system.

The threshold and intensity of reaction vary unceasingly even in the same individual; and they may be much influenced by the inhibiting effect of habit and education. Much of education is simply for the purpose of inhibiting reflex action and the somatic manifestations of psychic operations. Consequently, at the onset we must visualize the clinical picture as a shifting and kaleidoscopic drama. In addition, the pathologic pattern is often influenced or even transformed by additional environmental circumstances and secondary psychogenous factors. Therefore as soon as psychic causation is discovered, the mechanism of the psychic patterns must be studied, but without neglecting to investigate the physiologic and morphologic changes as well. For therapeutic purposes, these patients may be divided into the mild and, what experience has obliged me to designate as the "pernicious" cases of nervous dyspepsia.

The mild case, with its feeling of epigastric fulness, borborygmus, pyrosis, palpitation, abdominal distention, dizziness and headache, weakness of memory, cold hands and feet, anxiety relieved by the passage of flatus or the belching up of gas, its ribbon stools or scybalous feces, can usually be corrected by adjusting environmental circumstances and securing the control of the remaining psychoneurotic residuum. These cases do not die, but they are often prevented from following their normal mode of life.

Their fears of certain foods and similar phobias, and their interminable and reiterated complaints cause such annoyance to others that their home life is frequently ruined. The antagonistic family attitude reacts again on the patient; and this vicious circle results in such an aggravation of the condition as often to render it practically incurable. To tell such individuals that they are suffering from an over active imagination is not only imprudent but wrong. The medical attendant must remember that he is dealing with hypersuggestible material, weak in will, strongly influenced by emotion and not by reason. Such patients are often impatient, vacillating and hard to hold. Confidence is of prime importance and the most effective therapy is that which solves the psychic problem.

It is not intended here to discuss further these cases, nor the psychotic types of patients. What has urged me to choose the term "pernicious" in this paper is my concern for those cases of anorexia nervosa and vomiting which run a more or less malignant course and present a very grave prognosis.

The four cases that I present were all women in the third decade of life, and two of the four died.

CASE I

The patient was a private secretary who fell in love with her employer. It seems that he was unaware of this and quite suddenly married another woman. On learning the news, she lost her appetite and died 11 months later of extreme inanition. An autopsy was negative except for the incidental findings of inanition.

CASE II

A married woman, of extreme visceroptotic habitus, was told by her medical attendant that she had a positive Wassermann and subsequent investigation proved that her husband, to whom she was deeply attached, was the causative agent. Her romance was shattered and she went out to work determined to rid herself of her infection. Repeated serologic tests were negative, yet the phobia of a social disease was too strong to be suppressed. Esophagism soon developed, then sitophobia and eventually vomiting. This became so pernicious that ultimately nothing was retained. Emaciation developed to the degree of marasmus. A surgeon came in on the case and performed a gastroenterostomy on the theory that there was enough duodenal kink to justify it. The symptoms persisted, and even became worse. Several months later the patient died of inanition.

CASE III

The third patient was a woman who developed severe nervous anorexia and aerophagia with vomiting as a result of a severe sorrow. Complete aversion to food in any form resulted in extreme emaciation and bedsores. Duodenal alimentation was resorted to and the tube left well into the jejunum to prevent retrostalsis from bringing the liquid food into the stomach. After five months of difficult intubation, during which time death often seemed imminent, the patient recovered; but only because the time element succeeded in bleaching out the psychic factor.

CASE IV

The fourth case was a young woman who had undergone four abdominal sections for adhesions following a pus appendix operation. The resultant invalidism from

the procedures broke up a tentative engagement, her fiancé bluntly telling her she was too sickly to marry. Her chagrin at this rebuff actually improved her temporarily, and plans to marry a rival suitor whom she did not love were nearly completed. They were only thwarted by an attack of repeated vomiting, no food being retained at all. Anorexia and inanition rapidly set in until the patient fell to 67 pounds, her original weight being 140 pounds. Duodenal alimentation was attempted several times. It was rejected once by the patient who was quite resigned to die. A second trial resulted in the tube being vomited up and ultimately several intubations at short intervals of three to four weeks were successful. More than a month of continuous intubation invariably caused diarrhea. Over a year passed with little or no improvement, the tubal feeding alone keeping her alive. Two hospitalizations for study and consultative opinions yielded negative results. Roentgen-rays of the chest and gastrointestinal tract were negative. The basal metabolic rate was minus 18 and minus 22. Gradually the psychic trauma lessened, symptoms abated slowly and mouth feedings were stepped up to a rational intake. She ultimately reached 100 pounds, was able to be up and around, and 18 months later married the man of her choice who proved to be neither of the two former suitors. Although she showed a persistent amenorrhea for a year and a half, she eventually became pregnant and was delivered of a normal full term baby boy at St. Barnabas Hospital. She is well and happy today, weighing 155 pounds.

The remarkable thing about all these cases is, as Venables says, that no matter what the psychic cause may be, the complaints center entirely around food. Clow quotes Dejerine's statement that he has never seen a patient recover who loses more than half her weight. This observation is affirmed in the two fatal cases here cited. Another notable point is that a psychoneurotic heredity was absent in all these cases. Although all my cases were women, the literature, though scanty, shows that males are affected also. Berkman of The Mayo Clinic has given the most exhaustive analysis of any, reporting 117 cases, 28 of whom were males. Gull's three cases and 45 of Berkman's cases had amenorrhea. Cases 2 and 4 of mine had amenorrhea. Most of Berkman's cases had a lowered basal metabolic rate. My last case showed a minus 18 but neither thyroid nor suprarenal extract proved of any therapeutic value. Leede has indicted the suprarenal as the site of the chief endocrine disorder but this does not seem to be substantiated. Pain is rarely complained of and none of my cases exhibited this symptom. As soon as inanition sets in the pulse is slow and the blood pressure is low. Except for ptosis in case 2 the roentgenograms were negative. Gastric analysis in the early stages showed no abnormalities, but hypoacidity tends to develop with terminal exhaustion. Fecal tests were negative except for hemorrhoidal blood in one.

Diagnostically, the mild cases are distinguished by their lability of symptomatology. It is characteristic that the patient presents symptoms which do not fit within the bracket of the known diseases. The feeling of fulness and aerophagia may suddenly change to pyrosis, dizziness and headache with confusion and numbness of the extremities or tongue. But curiously, the pernicious type is stigmatized by the stability of symptoms. They begin with anorexia or vomiting or both and remain so until recovery or

death intervenes. The roentgenologic processes of duodenal stasis or reversed peristalsis as seen fluoroscopically continue with little change until convalescence ensues. Vomiting in the normal individual is a physiologic act usually preceded by more or less severe nausea and pallor with varying degrees of perspiration, weakness and confusion. In the pernicious type of nervous dyspepsia nausea is slight or absent. If present, it is of short duration unaccompanied by somatic perturbation and with no cold sweats or pallor. The patient shows, moreover, that the successive repetition of emesis develops a greater facility and ease of vomiting. Since nervous dyspepsia may, and so often does, accompany organic disease, all the probable organic affections must be excluded before risking the diagnosis of nervous dyspepsia of the uncomplicated type. Even at that, one cannot predict during the early stages which of his cases will run a benign or a pernicious course. As to the mechanism, one is impressed with what seems to be an inversion of vitality and an annihilation of the pleasure of life. Berkman epitomizes the long drawn out duration as follows: The loss of appetite following a certain psychic trauma is followed by inanition and consequent low rate of metabolism. This lowered rate appears to be a protective mechanism, for the tissues would be rapidly consumed and death more frequent than it is, if the rate were higher.

When treatment of the pernicious case is considered it must be remembered that all the ordinary methods are unsuccessful. It is useless to discuss the psychic trauma at first, as the prime indication is to prevent death. Intubation of the jejunum should be done at once. To put the bulb merely in the duodenum is to aggravate the case. Violent expulsive efforts frequently result with ejection of the tube and with the superadded symptom of nausea. It is because of the duodenal retrostalsis that the tube should be put well into the jejunum. In this way, hourly or two hourly feedings can be more readily tolerated and larger quantities of peptonized milk, with cream, lactose, egg and peptone additions, initiated. These feedings may be continued for a month or longer if necessary and may even have to be reinstituted if symptoms recur. When the tube cannot be tolerated on account of faucial irritation, or its passage will not be allowed by a refractory patient, the physician should not hesitate to have a jejunostomy done and kept open until recovery has occurred. Case 1 would have gotten well if this had been done, and case 2 should have had jejunostomy instead of gastroenterostomy. If tubal feedings alone do not control dehydration or acidosis, glucose by vein, skin or rectum may have to be resorted to.

The therapeutic use of insulin in stimulating appetite has been brought out by Bulatao and Carlson, Falta and recently by Nahum and Himwich. Berkman employed it in one of his cases but abandoned its further use because of lack of evidence of its effectiveness. It was attempted in case 4 but discontinued because of refusal of the mother to administer it. La-Barre's work demonstrates the reason for its failure in certain cases. Briefly, he showed that hypoglycemia initiated greater gastric muscular and

secretory action. Insulin by lowering blood sugar creates impulses in the brain which are conveyed by the vagus to the gastric musculature. These impulses increase peristalsis and this, reacting centripetally, registers in the field of consciousness as hunger. Accordingly, it can be inferred that insulin will be of service only in those cases in which it causes a hypoglycemia. Berkman claims that thyroid therapy is a valuable adjuvant measure because of the low basal rate. In spite of long continued use in case 4 it had only indifferent success.

When death has been prevented and inanition assuaged, then and only then comes the real time for psychotherapy. The removal of the psychogenetic factor, while of grave import, can not alone be counted upon to relieve the patient suffering from the serious type of this condition. Each case of pernicious nervous dyspepsia therefore must be considered from the individual standpoint.

To quote from S. I. Meltzer: "Lighter than air is psychotherapy. Do not practice it consciously. Have a thorough knowledge of your subject which entitles you to speak with conviction; have sincere sympathy which ought to manifest itself without obvious demonstration. Be practical in your advice and talk to the patient in common sense terms and you will have practiced psychotherapy honestly and successfully."

REFERENCES

- ALVAREZ, W. C.: Nervous indigestion, 1930, Paul B. Hoeber, New York.
BERKMAN, J. M.: Anorexia nervosa, anorexia, inanition and low basal metabolic rate, *Am. Jr. Med. Sci.*, 1930, clxxx, 411-424.
BULATAO, E., and CARLSON, A. J.: Contributions to physiology of stomach; influence of experimental changes in blood sugar level on gastric hunger contractions, *Am. Jr. Physiol.*, 1924, lxix, 107-115.
CLOW, F. E.: Anorexia nervosa, *New Eng. Jr. Med.*, 1932, ccvii, 613-617.
FALTA, W.: Insulin treatment and adipositas, *Wien klin. Wchnschr.*, 1925, xxxviii, 757-758.
GULL, W. W.: Anorexia nervosa (apepsia hysterica), *Trans. Clin. Soc. London*, 1888, vii, 22.
LABARRE, J.: Les fonctions contractiles et sécrétoires de l'estomac en rapport avec les variations du métabolisme glucidique, *Bull. Acad. roy. de méd. de Belgique*, 1931, xi, 598-651.
LEEDE, C. S.: Anorexia nervosa; hypoglycemia or hypoadrenia, *Northwest Med.*, 1928, xxvii, 233-238.
NAHUM, L. H., and HIMWICH, H. E.: Insulin and appetite; method for increasing weight in thin patients, *Am. Jr. Med. Sci.*, 1932, clxxxiii, 608-613.
VENABLES, J. F.: Anorexia nervosa; study of pathogenesis and treatment of nine cases, *Guy's Hosp. Rep.*, 1930, lxxx, 213-226.
VENABLES, J. F.: Anorexia nervosa, *Clin. Jr.*, 1930, lix, 544-548.

HEPATIC COMPLICATIONS IN THE TREATMENT OF SYPHILIS

THE ROSE BENGAL TEST AS A MEANS OF DETECTING DISTURBANCES OF LIVER FUNCTION AND ITS USE AS A GUIDE IN THE THERAPY OF SYPHILIS *

By GERSON R. BISKIND, M.D., NORMAN N. EPSTEIN, M.D., and
WM. J. KERR, M.D., F.A.C.P., *San Francisco, California*

PATIENTS undergoing routine antisyphilitic therapy occasionally develop hepatic disturbances. The liver of the individual with syphilis may be damaged by the disease or by untoward effects of antisyphilitic remedies, or by a combination of both. Latent disease of the liver may also be found in certain patients undergoing specific treatment, in whom the usual methods of clinical examination fail to reveal these pathologic processes. The clinical recognition of the acute phases of hepatic disease offers little difficulty. After the subsidence of the acute process, however, the determination of the exact status of the liver requires careful study.

ROSE BENGAL LIVER FUNCTION TEST

Many methods have been devised to evaluate the functional capacity of the liver in order to obtain some evidence of its morphologic state. In the Out-Patient Clinic for Syphilis in the University of California Medical School the rose bengal dye test has proved to be a reliable and practical method of studying liver function for the past 10 years. The dye, di-iodo-tetra-chlor-fluorescein, is eliminated from the blood stream only by way of the biliary tract. The rate of disappearance of rose bengal from the blood stream is proportional to the excretory function of the liver in the absence of mechanical obstruction to the bile ducts. The dye is nontoxic in the dosage sufficient for the test. It does not deteriorate on standing or upon sterilization. It is inexpensive, readily obtainable, and is not irritating to the veins. It is rapidly excreted only by the liver, and the color remains unchanged in the body during the period of observation so that it is easily detected in the blood plasma or serum. It has a slight photodynamic action on red blood cells. For this reason the patient is instructed not to expose himself to bright sunlight within two or three hours after administration of the dye. This is especially important if the dye is retained in the circulation for more than the usual period. No severe reactions have been encountered by us except in two patients who went directly into bright sunlight following injection of the dye. In these cases an edema of the face occurred which persisted for several hours.

* Received for publication October 23, 1933.

From the Division of Dermatology, the Department of Medicine and the Department of Pathology, University of California Medical School, San Francisco.

The exact technic of the test has been described recently¹ and need not be repeated in detail here. It is sufficient to state that 10 c.c. of a 1 per cent aqueous solution are injected intravenously over a period of 30 to 40 seconds. Blood samples are withdrawn at two, eight and sixteen minutes after the injection. The dye reaches its maximum concentration in the blood stream approximately two minutes after administration. This two-minute specimen is used as the standard against which the eight- and sixteen-minute specimens are compared. This procedure eliminates the error that is encountered by the use of an artificially prepared standard. The comparison is carried out at present by means of a comparing spectroscope¹ which eliminates certain errors found in the colorimetric method. The presence of biliary pigments or other substances which interfere with the matching of colors is no longer a hazard. From experience in several hundred cases, a retention in the blood stream of less than 55 per cent of the dye at the end of eight minutes, and 35 per cent retention at 16 minutes is considered normal. Retention above these figures is abnormal and indicates an abnormal function of the liver. According to the findings observed by the use of this test, the cases will be designated as having a normal, slightly abnormal, or a definitely abnormal liver function.

In 1926 one of us² reported the results of a liver function investigation among a number of patients with syphilis using the rose bengal dye test. These patients were young adults, for the most part, with early syphilis. The results revealed: first, that latent hepatic disease could be detected by the test; second, that in patients who have developed arsphenamine jaundice the liver function may return to normal upon clinical recovery; and third, that an arsphenamine dermatitis is not always associated with a disturbance of liver function.

OTHER LIVER FUNCTION TESTS

In the past 10 years this field of investigation has attracted many workers. The determination of bilirubin in the blood stream by the van den Bergh method is generally used as an indicator of liver function. Chargin and Orgel,³ Gerrard,⁴ Dixon, Campbell and Hanna,⁵ Irgang and Sala,⁶ and others using this method feel that the presence of a latent jaundice indicates damage to the liver, and that intensive antisiphilitic treatment should be stopped when this is present, but may be resumed when the bilirubinemia returns to normal. Generally, it may be said that the determination of bilirubin in the blood will indicate the onset of an icterus, and thus warn against continuing arsenical treatment, but that it fails to demonstrate slowly progressing damage within the liver.

Greenbaum and Brown⁷ used the phenol-tetra-chlor-phthalein dye test and found that a toxic icterus often leaves permanent dysfunction of the liver unassociated with clinical manifestations. Zieler⁸ states that the determination of urobilinogen in the urine can be used as an indicator of liver function.

PRESENT INVESTIGATION

The present investigation has been carried out upon patients in the Out-Patient Clinic for Syphilis at the University of California Medical School. For the most part they were older and had their infections for a longer period than the series reported in 1926. The investigation has the following objects:

First: To demonstrate latent liver dysfunction in the absence of clinical signs.

Second: To determine the degree of disturbance of liver function in patients with syphilis of the liver and to observe the effects of antisyphilitic therapy.

Third: To determine whether clinical recovery from an arsphenamine jaundice is always accompanied by complete return to normal of liver function.

Fourth: To determine the effect of long continued antisyphilitic therapy upon liver function.

CLINICAL MATERIAL

During the past three years the rose bengal test was performed upon 152 patients with syphilis. They were selected for study because they either were suspected of having hepatic involvement, or had developed jaundice at some time during the course of their treatment, or had been under antisyphilitic treatment for a long period of time.

CLASSIFICATION OF CASES

Of the entire group, 102 were males and 50 were females. They were in the age groups shown by table 1. The greatest number were between

TABLE I
Age Groups

Years	10-19	20-29	30-39	40-49	50-59	60-69	70-79
Male	0	5	30	28	27	9	3
Female	1	9	10	16	14	0	0
Total	1	14	40	44	41	9	3

30 and 60 years of age. When grouped according to the diagnosis made at entry, 13 were in the primary stage of syphilis, 11 were in the secondary period, 71 were classified as latent, and 57 as late, 21 of these latter having some form of syphilis of the nervous system.

I. UNTREATED GROUP:

Eleven cases were examined with the rose bengal test before antisyphilitic therapy had been administered. Eight of these showed a normal rate of excretion of the dye and presented no clinical evidence indicating hepatic disease. The three abnormal cases had enlargement of the liver and are listed in table 2. In two cases (70 and 156) the liver function

TABLE II
Untreated Group; Syphilis of the Liver

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Clinical Summary
					8 min.	16 min.		
70	51	M	Gummata of liver	8/10/31 9/28/31 12/22/31	81% 62% 67%	54% 50% 45%	Marked Moderate Moderate	Initial lesion in 1902. No antisyphilitic medication. Liver greatly enlarged and nodular. Following treatment with potassium iodide and bismuth there was marked clinical improvement. Left clinic.
128	40	F	Visceral syphilis	7/12/32 10/ 7/32 2/ 2/33 3/21/33 5/19/33	66% 65% 78% 72% 62%	50% 45% 52% — 40%	Moderate Moderate Moderate Moderate Slight	Initial lesion in 1909, treated with several mercury rubs. Spleen greatly enlarged, almost to iliac crest. Large irregular liver. No reduction in size of organs after treatment with potassium iodide and intramuscular injections of mercury salicylate and bismuth. Splenectomy on 12/10/32. Pathologic diagnosis: syphilis of liver and spleen.
156	48	M	Visceral syphilis	2/ 1/33 4/10/33	70% 64%	52% 42%	Moderate Slight	Primary lesion in 1914. No antisyphilitic medication. Subtotal thyroidectomy 1924 for exophthalmic goiter. Recurrence at entry. Preoperative Lugolization. Subtotal thyroidectomy. Examination at entry also revealed positive Wassermann, greatly enlarged smooth liver, palpable spleen; postoperative treatment with Lugol's solution produced decrease in size of liver and spleen before second rose bengal.

improved under therapy. Case 128 was of particular interest as a splenectomy was performed and we had an opportunity to study the liver and spleen grossly and microscopically. Antisyphilitic therapy administered before the operation did not reduce the size of the spleen or improve the liver function. Immediately following the splenectomy, the dye retention became greater, but later improved.

II. TREATED GROUP:

A. Those who had received little treatment.

Twenty-two patients received a small amount of antisyphilitic therapy before examination for liver function. In five cases the type of therapy was unknown as it had been given to the patient before entrance to the clinic. In 17 cases arsenicals had not been given; one received mercury and potassium iodide, and the other 16 mainly bismuth. Only one patient of this group showed an abnormal retention of the dye, and his record is listed in table 3. The treatment he received before entering the clinic consisted of two months of mercury rubs in 1924, and 20 intramuscular injections in 1930. Because of lack of clinical improvement on bismuth, the arsphenamines were tried cautiously, and the combination of drugs produced improvement in rose bengal excretion, but no clinical change.

Two patients (53 and 109) received arsenic only in the form of tryparsamide. The former had been given 35 grams of tryparsamide and 26 injections of bismuth before the first rose bengal test which was slightly abnormal. This was followed by 14 injections of mercury salicylate, 10 of bismuth, and 40 grams of tryparsamide. The next test showed practically no change. It is quite probable that in this case the impaired liver function was not produced by the tryparsamide, for its continued use did no further harm. The second patient was examined long after a small amount of tryparsamide had been given and showed a normal function.

B. Normal liver function—usual antisyphilitic treatment.

This group consists of 76 patients who received either arsphenamine or neoarsphenamine, and showed a normal rate of elimination of rose bengal. Table 4 lists the number of cases and the amount in grams of the arsphenamines given.

TABLE IV

Treated Group; Normal Liver Function						
Amount of arsphenamines	2-4 gm.	4-6 gm.	6-8 gm.	8-10 gm.	10-12 gm.	12-14 gm.
No. of cases	6	15	8	9	10	2
Amount of arsphenamines	14-16 gm.	16-18 gm.	18-20 gm.	20-22 gm.	22-24 gm.	
No. of cases	9	5	1	2	1	
Amount of arsphenamines	24-26 gm.	32-34 gm.	44-46 gm.			
No. of cases	1	1	1			
Total: 76 cases						
Average: 9.5 grams of the arsphenamines per patient.						

It is evident that a large amount of these arsenicals can be tolerated by some individuals without interfering with liver function.

TABLE III

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Clinical Summary
					8 min.	16 min.		
19	48	M	Cardiovascular syphilis	5/29/31 12/ 2/32 2/ 3/33	84% 80% 64%	58% 60% 44%	Marked Marked Moderate	<i>Examination:</i> Liver and spleen not palpable. Treatment before entry consisted of mercury rubs in 1924, and 20 injections of bismuth in 1930. Treatment after 5/29/31 consisted of 6.5 gm. of neoarsphenamine, 44 injections of bismuth, and potassium iodide. After 12/2/32 received 5 injections of bismuth.

TABLE V
Treated Group; Abnormal Liver Function; Never Jaundiced

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Clinical Summary
					8 min.	16 min.		
5	60	M	Visceral syphilis	3/ 2/32	80%	60%	Marked	Initial lesion in 1912 treated with mercury by mouth and as rubs. For 10 years up to a year before entry treated with 60 arsphenamine injections and 20 nearsphenamine injections. Liver and spleen palpable at entry. Between 9/11/32 and 3/3/33 given 4.3 gm. of nearsphenamine.
				3/23/32	76%	50%		
				8/23/32	65%	47%		
				9/11/32	64%	—		
				3/ 3/33	75%	57%		
16	48	F	Central nervous system syphilis	7/ 8/31	75%	50%	Moderate	Positive blood Wassermann and spinal fluid Wassermann 1931. Gastric crises. Treated with nearsphenamine 3.75 gm. and 12 bismuth injections. Died March 1932; perforated peptic ulcer.
				7/24/31	71%	41%		
23	38	M	Latent syphilis	3/23/32	60%	40%	Slight	Positive blood Wassermann in 1919. Treated with 12.3 gm. arsphenamine, 4.5 gm. nearsphenamine, 4.7 gm. mercury salicylate and mercury rubs up to 1923. Left clinic and returned in 1932; no treatment in the interval.
				1/20/33	80%	55%		
27	50	F	Latent syphilis	3/ 9/32	63%	37%	Slight	No history of infection. Routine examination revealed positive Wassermann and palpable liver. Treated with 36 injections of bismuth and 5.3 gm. of nearsphenamine before 3/9/32. 12 more bismuth injections before 12/14/32. One injection of nearsphenamine, 0.3 gm., before 2/10/33. No reaction.
				12/14/32	63%	42%		
				2/10/33	65%	43%		
48	38	M	Secondary syphilis	11/18/31	82%	46%	Moderate	Entered with secondary lesions, treated with 7.0 gm. of nearsphenamine and 12 bismuth injections before 11/18/31. Examination negative. Left clinic.
74	50	M	Central nervous system syphilis	9/ 9/31	75%	50%	Moderate	Treatment consisted of 5.05 gm. nearsphenamine and 11 injections of bismuth before 9/9/31. Followed by 12 injections of mercury salicylate and 1.55 gm. of nearsphenamine before 12/24/32. No reactions.
				12/24/32	80%	50%		

TABLE V—Continued

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Clinical Summary
					8 min.	16 min.		
99	51	F	Visceral syphilis	4/29/32 3/ 3/33	60% 70%	40% 40%	Slight Moderate	Positive Wassermann eight years ago, treated with 2.2 gm. arsphenamine. Palpable liver and spleen at entry. Treated with 12 intramuscular injections of mercury salicylate and then 2.05 gm. of neoarsphenamine. Slight clinical improvement. Liver and spleen not palpable on 3/3/33.
110	54	M	Latent syphilis	9/13/32	62%	44%	Slight	Treatment consisted of 43 gm. of neoarsphenamine and mercury rubs before entry. Liver palpable and extends 3 cm. below costal border. Present therapy is bismuth.
121	37	F	Latent syphilis	10/ 4/32	62%	40%	Slight	Two years of intensive treatment several years before entry, and 24 injections of bismuth and 10.5 gm. of neoarsphenamine just previous to entry.
131	52	M	Central nervous system syphilis	10/28/32 11/25/32	67% 62%	40% 40%	Slight Slight	Total treatment up to 10/28/32 was 9.2 gm. of neoarsphenamine and 47 injections of bismuth.
136	54	M	Central nervous system syphilis	12/24/32	68%	42%	Slight	Treatment before entry consisted of three injections of salvarsan 11 years ago followed by bismuth, mercury and potassium iodide at intervals. Examination at entry reveals a palpably enlarged liver.
145	27	M	Secondary syphilis	10/25/31 2/24/32 5/18/32 6/26/32	76% 64% 64% 65%	70% 35% 35% —	Marked Slight Slight Slight	Entered with lesions of secondary syphilis on 5/18/31. Treatment with 4.8 gm. neoarsphenamine and 12 injections of bismuth up to 10/25/31. Followed by 3.6 gm. neoarsphenamine and 12 injections of bismuth up to 2/24/32. Then 3.15 gm. of neoarsphenamine up to 6/26/32.
157	49	M	Latent syphilis; diabetes mellitus	2/ 1/33 3/17/33	67% 70%	45% 45%	Moderate Moderate	Chancere in 1902; no treatment until entry. Received 2.7 gm. neoarsphenamine and 10 bismuth injections before 2/1/33. Examination reveals an enlarged palpable liver.

TABLE VI
Treated Group; Jaundice; Recovery of Function

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Clinical Summary
					8 min.	16 min.		
14	20	M	Secondary syphilis	2/15/32 1/20/33	75% 55%	40% 33%	Moderate Normal	Onset of jaundice followed second injection of nearsphenamine. Lasted 4 weeks; cleared by 3/15/32. Subsequent treatment: 32 injections of bismuth and 5.7 gm. of nearsphenamine without ill effect.
15	37	M	Paresis	12/ 9/31 12/ 9/32	52% 40%	35% 28%	Normal Normal	Chancre in 1923. Intermittent treatment, totalling 12.4 gm. arsphenamine, 14 injections of bismuth and 75 of mercury salicylate up to 1929. Jaundice on 10/8/29 lasting three months. In 1930 treated with 20 injections of bismuth, 20 of mercury salicylate, 26 gm. of tryparsamide, and malarial therapy.
22	49	M	Central nervous system syphilis	11/20/30 1/27/31 3/ 5/31 9/23/31 11/25/32	80% 80% 69% 62% 57%	60% 52% 44% 37% 30%	Marked Marked Moderate Slight Normal	Chancre in 1910. Initial treatment consisted of 15 injections of bismuth started in March 1930. Nearsphenamine started on 8/5/30. Third injection followed by severe reaction. Onset of jaundice 9/10/30, lasting three months. Liver and spleen never palpable. Since October 1931 has had 34 gm. of tryparsamide.
44	37	M	Latent syphilis	2/15/32	58%	33%	Normal	Chancre in 1915. Treated with mercury and potassium iodide before entry. Given 22 injections of mercury salicylate at entry, then 2.05 gm. of arsphenamine. Jaundice Jan. 1 to 22, 1929. Liver and spleen not palpable. Therapy since then 3.6 gm. arsphenamine, 28 injections of bismuth, 9 of mercury salicylate. Died July 26, 1932 of hypertensive heart disease (no autopsy).

TABLE VI—Continued

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal		Degree of Abnormality	Clinical Summary
					8 min.	16 min.		
58	25	M	Primary syphilis	11/27/31	70%	56%	Moderate Normal Slight Normal Normal	Entered clinic Nov. 1931 with chancre. After 1.8 gm. of neoarsphenamine developed intense jaundice lasting three months. Since then has received 42 injections of bismuth, 13 of mercury salicylate, and 18 of bismarsen without ill effect.
				2/ 1/32	56%	30%		
				8/30/32	58%	37%		
				3/24/33	48%	26%		
106	18	F	Latent syphilis	5/18/32	56%	28%	Normal	Positive Wassermann in October 1931, treated with four injections each of neoarsphenamine and bismuth, followed by jaundice which had cleared by 3/18/32. Left clinic.
133	51	M	Late syphilis	12/ 9/32	53%	30%	Normal Normal	Chancre in 1904. Treated with mercury and potassium iodide in 1922, 18 injections of mercury salicylate and 4 gm. of arsphenamine in 1923. Left clinic; no further treatment. Returned in Sept. 1930 with intense jaundice and large palpable liver. Jaundice receded under potassium iodide and mercury by mouth. Started on bismuth in March 1932, followed by 1.8 gm. of neoarsphenamine and then bismuth. Liver decreasing in size.
				2/17/33	55%	—		
138	20	F	Secondary syphilis	1/20/33	50%	28%	Normal	Initial treatment consisted of 3.75 gm. of neoarsphenamine. Jaundice followed seventh injection on 10/5/32. Liver palpable, enlarged during jaundice, which lasted two weeks. Treated with bismuth since then.
158	26	F	Latent syphilis	2/10/33 3/31/33 5/25/33	65% — 50%	47% 38% —	Moderate Slight Normal	Positive Wassermann in Nov. 1932. Given 1.8 gm. of neoarsphenamine and two injections of bismuth. Marked reaction and jaundice followed the last injection of neoarsphenamine. Jaundice lasted three months, liver not palpable.

C. Abnormal liver function; no history of jaundice.

An abnormal liver function was found in 26 patients, none of whom gave a history of jaundice. These patients are divided into three classes: (1) those with definitely abnormal retention of the dye; (2) those with slight retention of the dye; and (3) those who were abnormal and later returned to normal. In table 5 are listed 13 cases where the patients showed a marked retention of the dye. Physical examination revealed a large palpable liver in six of these patients, and two of them also had a palpable spleen. Five received injections of arsphenamine after liver function studies had been performed and in three of these (5, 74, and 99) the retention became definitely worse, whereas in one (145) there was improvement, and in the fifth (27) there was but slight change. The 10 cases showing slight retention of the dye are not listed in detail as their exact status is difficult to determine. They will be kept under observation and reported upon at a later time. Three patients had a slightly abnormal retention of the dye at one time, and after further treatment the liver function test showed normal figures. Two of these three patients were tested after reactions to the arsenicals and this may account for the slight abnormality.

D. Abnormal liver function; history of jaundice.

Fifteen patients who had jaundice were studied. In 14 of these the arsphenamines probably played a decisive part in the production of the jaundice. In one case (51) the onset of jaundice was not due to treatment, but the patient is included in this group for convenience. He had received a moderate amount of antisypilitic treatment before liver function studies were made. The group is divided into three classes. In the first class are nine patients who showed a fairly rapid return to normal function after recovery from the jaundice. Table 6 shows the findings of this class. As was found in our earlier study, the young adult usually makes a complete recovery from the hepatitis and the arsenicals are often well tolerated later. All but one of these patients received less than four grams of the arsenicals before the onset of the jaundice. The next class consists of but two patients (52 and 67) listed in table 7. In the former, the liver function returned to normal after five years; in the latter it is not entirely normal after six years. These two patients probably suffered from a severe degree of liver damage which required a long period of time before the capacity of the liver was restored. The third class, listed in table 8, is made up of three patients who continue to have an abnormal retention of the dye following jaundice. In all three the syphilitic infection was of long standing, a large amount of arsenicals had been given previously, and a history of steady consumption of alcohol was obtained. This combination of factors probably produced some latent damage to the liver, which was followed by a more acute condition. In all three patients the liver was enlarged and palpable; one (95) had a typical cirrhosis, and this is suspected in case 56. The former died following a severe esophageal hemorrhage, and autopsy showed a toxic cirrhosis of the liver. The latter has been followed for three years

TABLE VII
Treated Group; Jaundice; Slow Recovery of Function with Slight Damage

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal			Degree of Abnormality	Clinical Summary
					8 min.	16 min.			
52	32	F	Early tabes dorsalis	9/-/28 2/-/30 3/-/31 7/-/32	84% 62% 70% 50%	58% 38% 59% 30%		Marked Slight Moderate Normal	Chancere in 1914. In 1919 treated with mercury and arsenicals. No other treatment until 1927, given 17 injections of mercury salicylate, 10 of bismuth and 3.45 gm. of neoarsphenamine. Jaundice in July 1928. Liver palpable 6 cm. below costal margin at that time. Treated with bismuth mainly since then. Liver not palpable in July 1932.
67	42	M	Latent syphilis	2/2/33	60%	35%		Slight	Chancere in 1919 and in following seven years treated at irregular intervals with arsenicals totalling 18 gm. of arsphenamine. Jaundice in 1927 one year after last treatment. Before entry in 1931 given three injections of neoarsphenamine. Attends clinic irregularly. Liver slightly enlarged.

TABLE VIII
Treated Group; Jaundice; Permanent Liver Damage

Case No.	Age	Sex	Diagnosis	Date	Rose Bengal			Degree of Abnormality	Clinical Summary
					8 min.	16 min.			
56	52	M	Late syphilis	11/30	90%	60%		Marked	Initial lesion in 1899; no treatment before entry in 1929. Alcohol taken in excess. Palpable liver at entry. Treatment: 7/29 to 9/29: 1.8 gm. arsphenamine and 22 injections of bismuth. 11/29 to 12/29: 2.4 gm. arsphenamine. 12/20 to 3/30: 14 injections of bismuth. 4/30 to 5/30: 2.1 gm. arsphenamine. 5/30 to 8/30: 12 injections of bismuth. 8/30 to 9/3/30: 1.8 gm. neoarsphenamine. Jaundice after injection on 9/3/30, lasted six weeks. 9/31 to 12/31: 12 injections of bismuth. 8/32 to 12/32: 18 injections of bismuth.
				12/30	83%	59%		Marked	
				1/31	83%	56%		Marked	
				3/31	66%	35%		Slight	
				4/31	71%	40%		Moderate	
				5/31	66%	43%		Slight	
				6/31	92%	76%		Marked	
				8/31	83%	66%		Marked	
				9/31	63%	43%		Slight	
				12/31	55%	37%		Normal	
				3/32	69%	46%		Moderate	
				4/32	62%	37%		Slight	
				7/32	66%	40%		Slight	
				8/32	62%	38%		Slight	
75	50	M	Latent syphilis	12/32	73%	45%		Moderate	Initial lesion in 1908, no treatment. Positive blood Wassermann in 1929. Treatment consisted of 14 injections of mercury salicylate followed by 3.6 gm. neoarsphenamine in July 1929. Left the clinic until April 1930, when he returned because of marked jaundice which lasted to Sept. 1930. Liver enlarged. Left clinic Nov. 1931.
				1/21/31	74%	45%		Moderate	
				4/ 2/31	55%	35%		Normal	
				9/ 7/31	66%	40%		Slight	
95	33	F	Visceral syphilis	4/20/32	88%	80%		Marked	Secondary lesions in 1926, treated intermittently with bismuth and arsenicals. Just before entry received 25 injections of neoarsphenamine followed by jaundice. History of excessive use of alcohol. Examination at entry revealed markedly enlarged liver, slightly enlarged spleen. Treated with potassium iodide and mercury salicylate. Numerous hemorrhages from esophageal varices before death on April 11, 1933 following massive hemorrhage. Autopsy: Pathologic diagnosis: toxic cirrhosis of the liver.
				5/18/32	88%	86%		Marked	
				2/ 9/33	82%	70%		Marked	

and tested frequently. There are periods when the excretion of dye approaches normal and periods when it is markedly delayed. These patients certainly have suffered permanent damage to their liver. Of the first group of nine patients, four have since taken courses of neoarsphenamine, one has had bismarsen, two have had tryparsamide, and one of these has also had malarial therapy. The two remaining patients have been jaundiced at such a recent date that, although they have normal liver function, they have not been treated as yet with the arsphenamines. The first seven patients indicate that when the dye excretion returns to normal the liver may tolerate the arsenicals without toxic effects.

COMMENT

The findings presented demonstrate that latent hepatic disease is not uncommon in patients under treatment for syphilis. In the entire series of 152 patients, 46 were found to have an abnormal liver function as demonstrated by protracted retention of rose bengal dye in the circulation. Seven of these patients presented other definite clinical evidence pointing toward a pathological process in the liver, and 13 had a history of jaundice. The remainder, or 26, had an impaired liver function which was detected only by the rose bengal test. This latter group may be definitely injured by the injudicious selection of antisyphilitic remedies.

Syphilis of the liver was found in but three patients, those listed in table 2. It was suspected in several others and probably played a part in the hepatic lesions of some, but this could not be proved. Of the three above mentioned cases, patient 19 showed marked improvement under treatment with potassium iodide and bismuth, and with this clinical improvement the retention of dye diminished. The patient listed as case 70 presents a diffuse hepatitis and will probably go on to a chronic state with cirrhosis. In the third case (156) there was improvement under treatment with potassium iodide.

As observed in a previous series of patients,² there is a return to normal function after an arsphenamine jaundice in the majority of cases. The age, the amount of arsenicals received, alcohol consumption and the previous state of the liver are some of the factors which determine whether a complete recovery of liver function will occur. The ability of these patients who do recover to be treated again with the arsenicals without producing clinical or laboratory evidence of impaired function strongly suggests that complete healing had taken place. In a certain percentage of cases permanent liver damage occurs and further treatment may be very harmful.

On many occasions an abnormal retention of the dye in conjunction with the history and physical findings has helped us to decide upon the type of antisyphilitic therapy to be instituted or resumed. Following an arsphenamine hepatitis as indicated by jaundice and an impaired liver function, the arsenicals are not administered until the dye excretion has been demonstrated to be normal. Indiscriminate treatment with arsphenamines can do these

patients considerable harm, notwithstanding the fact that in certain types of cases arsenicals should be given as soon as possible. The patient with early syphilis developing jaundice during the first course of arsphenamine is in urgent need of the arsenicals, and with recovery of liver function may again tolerate them.

The treated patients who showed evidence of liver damage received more of the arsenicals than those who showed a normal liver function. However, in this latter group there are many who have also been given large amounts of the arsenicals.

SUMMARY

1. The results of the rose bengal liver function test in 152 patients with syphilis are reported.

2. Latent hepatic disease was demonstrated in 26 patients by means of this test.

3. Large amounts of the arsphenamines may be tolerated without apparent ill effects upon the liver.

4. In the presence of latent hepatic disease the rose bengal liver function test is a valuable aid in the care of the patient with syphilis.

5. In 20 patients with clinical evidence of hepatic dysfunction the findings obtained with the rose bengal liver function test paralleled the clinical picture.

6. Although the majority of patients recover from an arsphenamine hepatitis a small number suffer permanent liver damage.

BIBLIOGRAPHY

1. ALTHAUSEN, T. L., BISKIND, G. R., and KERR, W. J.: The rose bengal test of hepatic function; a spectroscopic method, *Jr. Lab. and Clin. Med.*, 1933, xviii, 954.
2. EPSTEIN, N. N., and RAUSCHKOLB, J. E.: The rose bengal test for liver function, with particular reference to its use in therapy of syphilis, *Arch. Dermat. and Syph.*, 1926, xiv, 122-135.
3. CHARGIN, L., and ORGEL, S. Z.: Jaundice in syphilitic persons receiving arsenical medication, *Arch. Dermat. and Syph.*, 1923, vii, 495-498.
4. GERRARD, W. I.: The recognition of latent jaundice during treatment with arsenobenzol compounds, *Brit. Med. Jr.*, 1924, ii, 224-226.
5. DIXON, H. A., CAMPBELL, W. R., and HANNA, M. I.: Control of arsphenamine treatment by liver function tests, *Canadian Med. Assoc. Jr.*, 1926, xvi, 551-554.
6. IRGANG, S., and SALA, A. M.: The liver in active syphilis; a study of 179 cases of cutaneous syphilis, *Arch. Dermat. and Syph.*, 1930, xxi, 552-557.
7. GREENBAUM, S. S., and BROWN, H.: Phenol-tetra-chlor-phthalein liver test; in cases of acute and chronic syphilis under treatment and in various skin diseases, *Jr. Am. Med. Assoc.*, 1924, lxxxii, 88-91.
8. ZIELER, K.: Wird die Leistungsfähigkeit der Leber durch die Syphilisbehandlung geschädigt?, *Deutsch. med. Wehnschr.*, 1931, lvii, 393-397.

THE TREATMENT OF CIRCULATORY FAILURE*

By LOUIS M. WARFIELD, A.B., M.D., F.A.C.P., *Milwaukee, Wisconsin*

FOR YEARS investigators have been trying to unravel the processes which go on in the body following the initial shock of a violent injury, and further what takes place in the body in the condition known as secondary shock. A considerable measure of success has crowned the efforts, until now it is very generally agreed that not toxemia¹ but blood volume changes due to loss of fluid in the injured part play the chief rôle. With this concentration of blood there is also hypochloremia, low venous pressure, insufficient venous return flow to the heart and therefore rapid heart action and apparent circulatory failure. The practical application of the knowledge gained by the physiologists has lagged far behind. A great inertia takes hold of those who write textbooks so that it is often many years before radical changes, in methods of therapy particularly, become an integral part of the sections on treatment.

It would carry us too far to go into the details of the newer physiology of muscle contraction²; suffice it to emphasize that an adequate supply of three substances is essential for all muscle work—glucose, insulin, and oxygen.³ The heart muscle is no different from the skeletal muscles in its dependence upon these three substances. It differs fundamentally in several particulars. First, it is made up of cells which have no membrane around them comparable to the sarcolemma in skeletal muscle. Second, the nerve supply, so far as known, has no end-plates but is motivated by specialized nerve tissue. Third, a stimulus applied to the heart produces maximum contraction, however slight the stimulus may be. Fourth, the heart muscle is much less tolerant of oxygen debt than skeletal muscle and it is more sensitive to accumulation of lactic acid. It is like the skeletal muscles in that the strength of the contraction is dependent upon the initial length of the fibers, and also in that up to certain limits the more the fiber is stretched the stronger the contraction (Starling's law). In normal heart muscle it appears impossible to do permanent harm by any load placed upon it. The factors of safety in the body, particularly the vital capacity of the lungs and the sensitivity of the respiratory center to decreased pH of the blood,⁴ cause the whole body to stop before the heart muscle is damaged.

The adequate stimulus to ventricular contraction is diastolic filling which is dependent upon venous return flow. The normal state of the circulation depends upon the condition of the peripheral vessels (vasomotor tone) as well as upon the heart. There are further imponderable factors in the body which von Bergmann calls "humoral" and Fr. Kraus calls "protoplasm dynamics" which play a part in cardiovascular decompensation as well as the factor of oxygen exchange in the tissues themselves. No amount of extra

* Read at the annual meeting of the American Therapeutic Society, Milwaukee, Wisconsin, June 9 and 10, 1933. Received for publication September 14, 1933.

work so far as known causes the normal heart to hypertrophy, and the cardiac glycogen can not be reduced by any demand put upon it provided there is an adequate supply of oxygen.² The reserve is so great that, provided adequate supplies of oxygen, glucose and insulin are furnished, it performs extra work without becoming measurably hypertrophied. It is otherwise if the muscle is overstretched or damaged by some previous bacterial infection, or if the circulation in the coronary arteries is diminished while the muscle is being loaded. Eyster⁵ has shown that sudden overstretching of the normal heart of a dog by any method which rapidly increases diastolic volume will cause hypertrophy when the animal is immediately exercised to the point of exhaustion before time for compensation adjustment is given.

So far as our present knowledge goes acute dilatation of the heart is the result of anoxemia⁶ (this is contrary to the statement in most textbooks) or of excessive load on an already damaged heart. Acute dilatation does not occur in febrile infections when the heart was previously undamaged, except in the antemortem state when anoxemia supervenes.

For convenience, circulatory failure may be divided into (a) central and (b) peripheral; but no clear cut distinction can be made, and as a matter of fact the whole cardiovascular system is a unit and cannot be separated too sharply into its two chief parts. Yet, as a matter of clinical as well as experimental knowledge, one or the other part usually fails first. It is then often possible at the bedside to evaluate the more important feature of the failing circulation. No intelligent treatment can be administered unless there is understanding of the factors which produce, on the one hand central or heart failure, on the other hand peripheral failure.

It is well known that all the blood in the body is not in active circulation under conditions of ordinary life.⁷ What Krogh demonstrated for muscle and Richards for kidney glomeruli is true for the body as a whole. The value of 75 to 85 c.c. of blood per kilogram of body weight as the blood volume of a resting, fasting, recumbent person represents only the "effective" volume. How much blood is stagnant or very sluggishly circulating in the various depots of the body is a matter of pure guess. Since Barcroft described the spleen of the dog as the important depot in that animal, whence a considerable amount of blood could be rapidly thrown into circulation, increasing attention has been paid to the storage areas in the human body. Eppinger⁸ conclusively proved that in man the spleen was of no importance as a depot. Wollheim⁹ has shown that the subpapillary capillary plexus of vessels in the skin is probably the most important depot under ordinary conditions. The splanchnic area has long been known to be a huge bed capable of containing a large part of the blood. These are the two most important depots. The liver is to be considered also as well as the lungs under certain pathological conditions.

The subject of heart failure would seem to be rather a trite one except for the fact that new concepts are being established which possibly give us a little better understanding of the condition and a basis for more rational

methods of treatment. Within the past few years, in 1928, Wollheim,^{10, 11} as the result of work in von Bergmann's clinic, divided cardiac decompensation into two groups which he called plus and minus decompensation. His reason for this division is that he found in certain cases that the blood volume was definitely increased, while in other cases it was definitely decreased. Eppinger and Schürmeyer,⁸ using the CO method of estimating blood volume, showed that hypertonics have already in circulation a larger blood volume than normal and this is not increased much by exercise or the application of heat, in contrast to the man with normal pressure whose blood volume under such conditions increases 15 to 20 per cent.

The chronic plus decompensation cases, which are the most common, are those whose breakdown is the result of excessive strain such as occurs in hypertonia, in aortic insufficiency, and in most cases of mitral stenosis especially when combined with insufficiency and a large left ventricle.

The chronic minus decompensation cases are seen in primary disturbances in oxygen exchange in the lungs, in pulmonary stenosis, pulmonary sclerosis, not infrequently in mitral stenosis, in emphysema, and in thyrotoxicosis. In the acute form they are seen in lobar pneumonia, in the bronchopneumonia of grippe, in toxic infectious diseases and in circulatory shock. The blood volume may be as low as 40 to 50 c.c. per kilogram of body weight.

The plus cases are characterized by dyspnea, orthopnea, edema, distention of the veins in the neck, and cyanosis, especially of the lips and acral parts. Pressure of the liver, as Plesch showed, increases the distention of the veins on the right side of the neck. These patients are more comfortable when sitting up with the legs hanging down as the blood volume is then reduced from 400 to 1000 c.c. (Wollheim), by the filling of the subpapillary skin plexuses of the legs.

The most striking characteristic of the chronic minus cases is the absence of dyspnea when at rest. These patients are comfortable lying flat in bed. There is no distention of the neck veins. Cyanosis is found in patches in the skin. The blood pressure is not much, if any, decreased below the normal figure in compensation because the arterioles still retain their tone. It may even be higher than in the compensated state.

Such cases are considered to be instances of vascular insufficiency with blood held back in the depots, in contradistinction to cardiac insufficiency where more blood is actually in circulation.

As most of the cases of central cardiac failure which are seen in patients are those of plus decompensation, the treatment is that well recognized for such cases, namely: digitalis in adequate dosage, strophanthin (ouabain) in certain emergency cases, venesection, diuretics, carbohydrate diet limited in amount. Under certain conditions the oxygen tent or oxygen chamber is of great value. Wiener¹² has recently called attention to the value of small doses of insulin followed by intravenous glucose, 50 to 200 gm., in the treatment of these cases. It is known that glucose is used up in heart muscle in

direct proportion to work done. It has also been shown that there is increased lactic acid in the blood in these failing hearts^{3,13} and it is known that the heart muscle is quickly poisoned by a very slight excess of lactic acid. The sluggish coronary circulation leads to anoxemia and thus to the consequent dilatation with further decrease in stroke and minute volume. The administration of oxygen, glucose and insulin is logical treatment and has a sound experimental basis.

The treatment of the minus decompensation cases, those characterized by lessened blood volume, presents an entirely different problem. While Wollheim is probably correct in dividing the cases as he does on the basis of much careful work, yet one must bear in mind that a sharp distinction cannot always be drawn between cardiac and vascular insufficiency. There is, for example, minus decompensation in infarct of the heart, in subacute bacterial endocarditis, often in recurrent rheumatic endocarditis and in malignant endocarditis. These are cases of cardiac failure where there is definite damage to the heart, yet the blood volume is low. The collapse is not peripheral but cardiac. The venous pressure is low. As digitalis decreases blood volume even in normal persons¹¹ and further reduces venous pressure it obviously would be contraindicated.

There are cases, however, of chronic minus decompensation seen chiefly in the cardiovascular breakdown of thyrotoxicosis where patients are not usually dyspneic, where venous pressure is not high, where there is no cyanosis or the cyanosis is distributed in patchy areas over the skin. In spite of the fact that the arrhythmia present is practically always auricular fibrillation, experience has shown that digitalis has but little effect upon the symptoms and signs. Subtotal thyroidectomy, preceded by iodine administered in some form, is the most successful treatment known at the present time for this type of cardiac failure.

I wish to direct particular attention to the treatment of the cases of so-called heart weakness which often comes on in the course of most of the infectious fevers when the patients are seriously ill. But before discussing the treatment some reason must be given for the rather unusual conclusions which will be drawn.

If one looks in the recent textbooks of medicine or therapeutics under the sections on treatment of the various infectious fevers, he will find the statement that the heart fails and that the heart should be stimulated. Practically all advise digitalis in some form, some extolling it as the ideal heart stimulant (Beckman), others saying that some give it prophylactically at the onset of fever, especially in pneumonia and that some do not (Musser). Nowhere does one find any other idea expressed but that the heart fails.

Now let us examine these two, one might almost call them axioms in the light of modern physiological knowledge. First, as to the statement that digitalis is a valuable heart stimulant it may be said that all the information we now possess is that digitalis is not a heart stimulant. Its action is primarily upon the vagus nerves and upon the junctional tissues. Further it

reduces blood volume and may have some dilating action on the coronary arteries, but that is doubted.¹⁴ True, in toxic doses it causes the heart to go into tetanic contraction due probably to the direct action of digitoxin upon the muscle. Holzbach¹⁵ states that it is senseless to give digitalis for the purpose of protecting the heart. Randolph¹⁶ has criticized the routine treatment of pneumonia with digitalis, stating his belief that it is ineffective and indeed not infrequently injurious. Christian¹⁷ believes that digitalis does have some tonic action upon large hearts, tending to protect them from further dilatation. In this sense it may be called a heart stimulant but the hypertrophied heart is not the heart in a patient with serious infection.

The next belief is that the heart fails in cases of serious infection. But does the heart fail as the initial circulatory symptom? Holzbach, Randolph, Wollheim, von Bergmann, Romberg and Passler, and many others say emphatically that the heart itself does not primarily fail in such diseases. It has been found in cases of secondary collapse in peritonitis that several conditions develop: (1) there is low blood volume due to loss of fluid into the tissues; (2) there is concentration of the blood; (3) there is loss of chlorides in the blood; and (4) there is low venous pressure. It is known that the heart has an enormous reserve force, that given oxygen, glucose, and insulin it is practically impossible to wear it down. It is known that stimulus to contraction comes from adequate diastolic filling. It is known that a certain head of pressure must be maintained in the coronary arteries in order that the organ may do its work. The deleterious effects of dehydration and of disturbed mineral balance are beginning to be appreciated. In fevers when the heart apparently fails the four conditions cited above are all present.¹⁸ It would therefore seem that the so-called heart failure is quite comparable to the condition described as secondary shock. It has nothing to do with the heart primarily but the effect upon the heart is necessarily profound. The decreased blood volume leads to decreased venous return flow so that the heart is not dilated but is smaller than normal. The vasoconstrictor center in the medulla is stimulated so that the arterioles contract while the capillaries dilate due to the histamine-like substances produced by breaking down of the proteins by the bacterial toxins. In this stage the blood pressure is not materially changed, as I have repeatedly found. The venous pressure is probably low. However, the low blood volume and insufficient venous return flow cause the heart to beat faster in order to keep the minute volume sufficient to carry on the circulation. If the circulatory failure is greater the blood volume becomes less, the heart beats faster, the pulse becomes smaller, and the blood pressure falls. A point is reached when there is not diastolic pressure sufficient to keep circulation in the coronary arteries. Anoxemia of the muscle results, lactic acid is not carried away, it poisons the heart, and the muscle dilates. At autopsy the pathologist finds a dilated right heart and concludes that dilatation of the heart was a factor in the death. It is true, but that is a condition brought about very shortly before death.

The actual effects of the decrease in blood chlorides is not definitely known. It probably has to do with disturbances in acid-base equilibrium and would suggest alkalosis, yet determinations of the alkaline reserve in pneumonia have not shown any consistent changes from the normal. The blood chlorides appear to be necessary for phagocytosis. Fleming¹⁹ has shown that very slight increase, as little as 0.01 per cent, greatly stimulates phagocytosis.

Consider what usually happens when a person acquires some serious infection. Previously in good health, within a few days or a week or two his heart apparently wears out. In the light of what we know of the heart this seems quite incomprehensible. What we can understand is that as a result of the toxic products of bacteria the proteins of the tissues are broken down resulting in an increased osmotic pressure which draws fluid from the capillaries thus reducing blood volume.²⁰ In the infectious fevers some such process as the following probably takes place. "As the provocative poison reaches the tissues (perhaps the muscles in particular) catabolic changes are initiated which increase the affinity of the tissues for water. This general demand upon the blood for water tends to reduce the blood volume, especially at the expense of the surface blood. The skin immediately becomes cooler, and this arouses the nervous regulation against cold, thus exaggerating the processes of vasoconstriction and hemo-concentration. This continues until the blood becomes warm enough for the nervous centers to interpret the temperature as comfortable or neutral." (Barbour.) With reduced circulating blood volume and concentration of the blood, diastolic filling is profoundly disturbed. The heart speeds up its rate; its nutrition suffers. The peripheral circulation then is the source of the initial circulatory failure which most people until recently have ascribed to the heart.

Emphasis must be placed on the idea that the heart does not fail. Romberg and Passler²¹ years ago showed that even in most severe experimental infections in rabbits the functional capacity of the heart does not suffer. If the conditions listed above which bring about the so-called heart failure could be brought back to normal, the heart would be found to be carrying on as usual. Recovery from disease means the return to normal blood volume, normal chlorides, normal concentration of blood, normal venous pressure.

TREATMENT

More than 20 years ago when typhoid fever was so prevalent, I thought that by using gravity to assist in venous return I might combat what appeared to be circulatory collapse. Hence when the pulse began to be increased I elevated the foot of the bed about 10 inches. That often proved sufficient treatment. If the circulatory failure became greater, the patients' legs were bandaged from the ankles to the hips. I knew nothing of measurements of blood volume then, but recent studies by Wollheim²² show that these procedures increase circulating blood volume. Fluids were pushed, high carbohydrate diet given, and every effort made to keep the patient from

losing weight. Those days are over but there are other serious infections to be treated and the problem in such cases is still how to treat the failing circulation in the most rational way.

No experimentation is more difficult than that in the clinic on human subjects. Control cases exactly similar to those treated in any special manner are not possible to secure. By the omission of the special treatment in alternate cases an approximate control series can be obtained, but such alternate cases are not true experimental controls. Further, the human being is so constructed that one gets well in spite of what is done, another dies in spite of what is done. Yet there should be principles of proper treatment and it is to these principles that we now turn.

What have we to do, and what means have we with which to do what should be done?

Obviously circulating blood volume should be increased and the chloride content of the blood should be raised. To achieve these results we have certain drugs and the use of fluids by intravenous administration. As digitalis decreases blood volume its use is absolutely contraindicated except in cases where auricular fibrillation exists. The so-called vasomotor drugs increase the circulating blood volume. Into this class fall camphor and its substitute preparations, Cardiozal and Hexaton, and likewise caffein, strychnine and Ephetonine. Graphic results of experiments in the clinic are published by Wollheim.¹⁰ The most useful drug in my hands has been strychnine sulphate. It is said to increase blood volume (Wollheim). It should be given in large doses hypodermically (gr. 1/15 to 1/10 to an adult every hour or two). This may seem heroic and not devoid of danger. Yet I have given gr. 1/10 hypo. every hour for 36 hours; there was no evidence of strychnine poisoning, and the patient, desperately ill with typhoid fever, recovered. The strychnine may have had no part in her recovery. Caffein-sodium benzoate and camphor preparations such as Metrazol are said to increase blood volume but also are said to stimulate the vasoconstrictor center in the medulla. These drugs were highly extolled before it was known that in circulatory collapse the center is in a state of increased tone. Personally I have not used these drugs for some time. Adrenalin, ephedrin and pituitrin are recommended. In sudden collapse I have used both adrenalin and pituitrin with apparently good result. The action of both is transient, especially adrenalin. Pituitrin (pitressin) is said to have a too violent constrictor effect. Adrenalin may be given in the fluid of intravenous transfusion with saline or glucose or the combination of the two.²² This prolongs its action and simulates in some degree natural processes.

The most logical and satisfactory method of increasing blood volume is by introducing fluids intravenously. Normal saline with glucose (dextrose) is always on hand. "Dextrose, intravenously given, resembles the antipyretics in that it reduces the temperature in fever, causing the blood to become more dilute than under normal conditions. This supports the contention that blood sugar plays a rôle in antipyretic action."²⁰ It should be

given in large quantities, three to four liters or more in 24 hours. A resting, fasting person loses about three liters of fluid daily. We live in water. The consequences of even mild dehydration are serious. Many use glucose and saline but are content with a liter a day. I would urge larger quantities for obvious reasons. But saline-glucose has a decided drawback. The fluid does not remain in the blood for long but is drawn out into the tissues. The effect is not lasting. What is wanted is a fluid which contains colloids which will not only remain in the vessels but which may withdraw fluid from the tissues into the vessels. Naturally the ideal fluid is blood itself or blood plasma. Blood has been used repeatedly but the reasons usually given for its good effects included the supposed action of antibodies. The real reasons are that it not only increases and maintains blood volume, introduces important ions such as Ca, Na, K, but it adds oxygen carrying red blood cells. This last is not so important if there is no anemia. Lastly, it has been shown that acacia solutions also have the property of maintaining blood volume. Barbour and Baretz found that acacia similarly tends to dilute the blood in fever and to reduce the temperature, which it does not do in normal animals. Now there is available acacia solution which can readily be diluted to the proper 6 per cent by the addition of distilled water. This also has chlorides in solution. Not enough experience has accumulated so that we know how much or how often acacia solutions should be given. Practically it would seem that the amount could be controlled by hematocrit readings. These have now been simplified so that any laboratory should be able to perform them. This is a clinical problem which must be worked out. Since ill patients have recovered without these transfusions it would be sensible to err on the safe side and give not more than 500 c.c. of blood (citrated or whole) or 500 c.c. of 6 per cent acacia solution every three to four days. In the meantime one should give daily intravenous transfusions of glucose and saline in large amounts and very slowly to reduce the possibility of "speed shock."

SUMMARY AND CONCLUSIONS

Cases of circulatory failure may be classified into two groups: (1) central, and (2) peripheral. The former is usually accompanied by increased blood volume, the latter by decreased blood volume. This does not hold true where the heart muscle is acutely damaged as it is in coronary occlusion or in purulent embolism of the smaller coronary arteries or in acute rheumatic heart conditions.

The first group, called plus decompensation, is characterized by dyspnea, orthopnea, cyanosis of lips and acral parts, and increased venous pressure. The second group, called minus decompensation, has low blood volume, no dyspnea on lying down, patchy skin cyanosis, and low venous pressure. This last group includes fewer chronic cases than does the first group. The circulatory failure of thyrotoxicosis is the most commonly seen chronic form of minus decompensation. These two groups can usually be recognized at the bedside.

The acute cases of minus decompensation correspond to circulatory failure in all the severe infections. It is peripheral circulatory failure, not failure of the heart itself, and in this failure the following four conditions are found: (1) decreased blood volume and insufficient venous return flow; (2) hemoconcentration; (3) decreased blood chlorides; and (4) low venous pressure. Arguments are advanced to prove that this condition is that of so-called secondary shock.

Since this is true, it follows that the heart itself does not fail in infections until just before death. The measures which are very widely used to stimulate the heart in infections must be futile: first, because the heart is not functionally impaired even in severe infections; second, because we know of no real heart stimulant even if we desired to stimulate the heart itself.

The treatment of the plus decompensation cases is that commonly employed for cardiac decompensation.

The treatment of the minus decompensation cases should be directed toward correcting the four conditions listed above. In certain cases the head-down position and crowding fluids by mouth will suffice. In general, saline solution and 10 per cent glucose should be given intravenously (very slowly to avoid "speed shock"), in amounts up to 3 to 4 liters or more daily. Also one can use transfusions of whole or citrated blood or 6 per cent acacia solution. Probably these transfusions should not be used in amounts greater than 500 c.c. and at 3 to 4 day intervals.

Drugs to be recommended are those which increase blood volume. These are strychnine in adequate doses, caffein sodiobenzoate, Metrozal, adrenalin and pitressin. Adrenalin may be added to the saline-glucose transfusion.

Digitalis is considered to be contraindicated chiefly because it decreases blood volume.

BIBLIOGRAPHY

1. BLALOCK, A., BEARD, J. W., and JOHNSON, G. S.: Experimental shock; a study of its production and treatment, *Jr. Am. Med. Assoc.*, 1931, xcvi, 1794-1797.
2. HILL, A. V.: Revolution in muscle physiology, *Physiol. Rev.*, 1932, xii, 56-67.
3. MEAKINS, J. C.: Modern muscle physiology and circulatory failure, *ANN. INT. MED.*, 1932, vi, 506-513.
4. HENDERSON, Y., and RADLOFF, E. M.: Chemical control of breathing, as shown in acid base balance of blood, under progressive decrease of oxygen, *Am. Jr. Physiol.*, 1932, ci, 647-661.
5. EYSTER, J. A. E.: Experimental and clinical studies in hypertrophy, *Jr. Am. Med. Assoc.*, 1928, xci, 1881-1884.
6. KATZ, L. N., and LONG, C. N. H.: *Proc. Roy. Soc., Series B.* 1925-1926, xcix, 8.
7. VON BERGMANN, G.: Zum Problem der Kompensation und Dekompensation des Kreislaufs, *Deutsch. med. Wchnschr.*, 1930, lvi, 553-556.
8. EPPINGER, H., and SCHÜRMEYER, K.: Über den Kollaps und analoge Zustände, *Klin. Wchnschr.*, 1928, vii, 777-785.
9. WOLLHEIM, E.: Zur Funktion der subpapillären Gefäßplexus in der Haut, *Klin. Wchnschr.*, 1927, vi, 2134-2137.
10. WOLLHEIM, E.: Kompensation und Dekompensation der Kreislaufs, *Klin. Wchnschr.*, 1928, vii, 1261-1265.

11. WOLLHEIM, E.: Zum Problem der Kompensation und Dekompensation der Kreislaufs, *Deutsch. med. Wchnschr.*, 1930, lvi, 556-560.
12. WIENER, J.: L'insulinothérapie dans les affections cardiaques, *Bruxelles méd.*, 1932, xiii, 188-191.
13. EPPINGER, H., LASZLO, D., and SCHÜRMEYER, A.: Über die mutmasslichen Ursachen der Unökonomie im Herzfehlerorganismus, *Klin. Wchnschr.*, 1928, vii, 2231-2239.
14. GILBERT, N. C., and FENN, G. K.: Effect of digitalis on coronary flow, *Arch. Int. Med.*, 1932, 1, 668-683.
15. HOLZBACH, E.: Die toxische Kollaps und seine Bekämpfung, *Munchen. med. Wchnschr.*, 1930, lxxvii, 11-12.
16. RANDOLPH, B. M.: Cardiovascular problem in pneumonia, *Arch. Int. Med.*, 1929, xliii, 249-266.
17. CHRISTIAN, H. A.: Use of digitalis other than in treatment of cardiac decompensation, *Jr. Am. Med. Assoc.*, 1933, c, 789-792.
18. MACLEOD, J. J. R.: *Physiology and biochemistry in modern medicine*, 5 Ed., 1926, C. V. Mosby Co., St. Louis.
19. FLEMING, A.: Effect of variations of salt content of blood on its bactericidal power, in vitro and in vivo, *Brit. Jr. Exper. Path.*, 1926, vii, 274-281.
20. BARBOUR, H. G.: Heat-regulating mechanism of body, *Physiol. Rev.*, 1921, i, 295.
21. ROMBERG, E., and PASSLER, H.: Untersuchungen über die allgemeine Pathologie und Therapie der Kreislaufstörung bei acuten Infektionskrankheiten, *Arch. f. klin. Med.*, 1899, lxiv, 652.
22. SCHOTTMUELLER: Zur Behandlung der Kreislaufschwäche bei akuten Infektionskrankheiten, insbesondere bei der kruppösen Pneumonie, *Deutsch. med. Wchnschr.*, 1928, liv, 1538-1539.

SPOROTRICHOSIS

REPORT OF A CASE ORIGINATING IN NEW YORK*

By GEORGE M. LEWIS, M.D., and J. HOMER CUDMORE, M.D., F.A.C.P.
New York, N. Y.

IN A recent publication, Hopkins and Benham¹ reviewed the incidence of sporotrichosis in New York State, and found that only one culturally proved case had been reported previous to their communication. The first case was presented by Howard Fox² before the New York Academy of Medicine in 1921. The patient was a sailor and probably acquired the disease in the tropics. The two cases reported by Hopkins and Benham¹ included one observed by Osborne in Buffalo in 1928, and one studied by them in New York City in 1929. The second case probably developed the infection in Monticello, New York. Cases having clinical evidence in favor of the diagnosis of sporotrichosis were reported by Turrell,³ Lapowsky,⁴ Wise⁵ (in whose case the symptoms were typical) and Walzer.⁶ Mount's⁷ report of an unusual type of sporotrichosis, although of great interest, was unfortunately deficient in laboratory confirmation.

CLINICAL TYPES OF SPOROTRICHOSIS

1. *Localized Lymphangitic.* Most of the reported cases in the United States fall into this group in which a primary lesion or chancre appears on an exposed part of the body. This lesion is indurated; softening and abscess formation may take place; an indolent ulcer may develop or it may vegetate. Rarely the disease remains localized to this single lesion. Usually, after a week or more, a painless ascending inflammation develops in the regional lymphatics along the course of which secondary nodules form and undergo similar changes to those noted in the chancre. Regional lymph node enlargement is uncommon (an important diagnostic point in the clinical differentiation from tularemia, in which latter disease lymph node enlargement is a constant finding). Systemic symptoms or involvement are uncommon. There is little if any tendency to spontaneous recovery. Scarring of varying degrees of severity remains when the lesions involute.

2. *Disseminated Subcutaneous.* In this variety, commonly observed in France, small, hard, painless, subcutaneous nodules of varying number appear in scattered locations over the body. Within three to six weeks, the skin becomes involved, the central part of the nodule softens and forms an abscess which may discharge if traumatized, forming a cup-shaped ulcer with a firm indurated border. New lesions may continue to appear indefinitely in the untreated patient.

* Received for publication August 4, 1933.

From the Department of Dermatology and Syphilology, New York Post-Graduate Medical School and Hospital, Columbia University, Dr. George M. MacKee, Director; and the Manhattan General Hospital.

3. *Disseminated Ulcerating*. Although similar to the preceding type, this form is distinguished by a tendency to early spontaneous ulceration of the lesions. The ulcerations vary in size and character a great deal. At times large crateriform ulcers develop simulating tuberculosis or tertiary syphilis. There is little if any tendency to spontaneous cure. In the untreated patient the general health may become impaired, with the appearance of symptoms of toxemia.

4. *Epidermic*. The primary lesion in sporotrichosis is practically always subcutaneous. In some instances the epidermis at adjacent or remote sites becomes secondarily infected, papules, pustules and small ulcers developing. Rare cases have been described in which the disease is limited to the skin, and in such instances tuberculosis is differentiated with difficulty. The mucous membranes may also become secondarily infected in cases of the disseminated or ulcerating varieties. The organism is said to be capable of remaining as a saprophyte in the mouth or other mucous surfaces after the disease is apparently eradicated, rendering the patient a possible "carrier."

5. *Systemic*. At times the sporotrichium invades the deeper tissues and organs. In the majority of instances this occurs in the disseminated varieties when treatment is not promptly instituted. The differential diagnosis must exclude cancer, syphilis, tuberculosis and other infections as the etiological factor. The bones or joints may be affected, the tibia being the most common site of the infection. Invasion of the muscles and glandular structures may occur and a number of instances of pulmonary involvement have been reported. Although a common site of involvement in laboratory animals, the epididymis is rarely affected in humans. Gastrointestinal and cerebrospinal involvement is said to be extremely uncommon.

In the following report, which we believe describes the fourth culturally proved case of sporotrichosis originating in New York State, the patient had not been out of New York City for many months prior to the onset of the disease.

CASE REPORT

History. Miss E. H., aged 34, single, an office worker, was first seen on January 27, 1933. There were six granulomatous lesions on her right arm. The first lesion appeared four months previously on the extensor surface of the forearm (figure 1) as a small reddened point of indefinite nature, gradually increased in size, became pustular and finally formed a subcutaneous abscess. Within a month the five other lesions progressively appeared along the arm, the last one approaching the axilla. (Figure 2.) The patient had not handled raw fruit, vegetables, or flowers, nor had she come in contact with animals. She had worked in the garden a few days previously, transplanting some cactus plants. While there, she wore rubber gloves. The initial lesion was above the skin covered by the gloves but she was unable to recall any scratch or abrasion. The lesions were all incised with the exception of the last one. Despite the good drainage so established and the continuous use of wet dressings and antiseptic washes, healing did not take place. The lesions were not painful.

Examination. The patient was well nourished, being about five feet six inches tall and weighing 160 pounds. The temperature was normal and the pulse rate was

72. She appeared to be in vigorous health. On the right arm were six cutaneous and subcutaneous well-defined tumefactions (figures 1 and 2), the largest being the initial lesion. This was situated on the extensor surface of the forearm, three inches above the wrist. The lesion was irregular in outline, of a dusky red appearance at the periphery and exhibited an ulceration in the mid portion. Thick ropy pus covered the ulcer and could be expressed from two sinus tracts present in the outer part of the lesion. Exuberant granulation tissue was visible at the base and bleeding was readily produced when this tissue was but lightly touched. On palpation, the mass was firm



FIG. 1. Sporotrichotic chancre.

but not cartilaginous and was freely movable. The remaining five lesions were smaller, were soft on palpation and had central openings from which thick, yellowish-white pus exuded; they were more superficial than the primary one. No pain or tenderness was noted upon manipulation. The masses were joined by a well defined and distinct lymphangitis but there were no palpable lymph nodes.



FIG. 2. Secondary sporotrichosis lesions.

Cultural Findings. No fungi were found upon direct examination of secretion despite numerous attempts. At a later date, when the patient was under treatment, the process was repeated, using the technic advised by Lawless,⁸ but without success. On culture, at room temperature, using Sabouraud's glucose media, fungus colonies

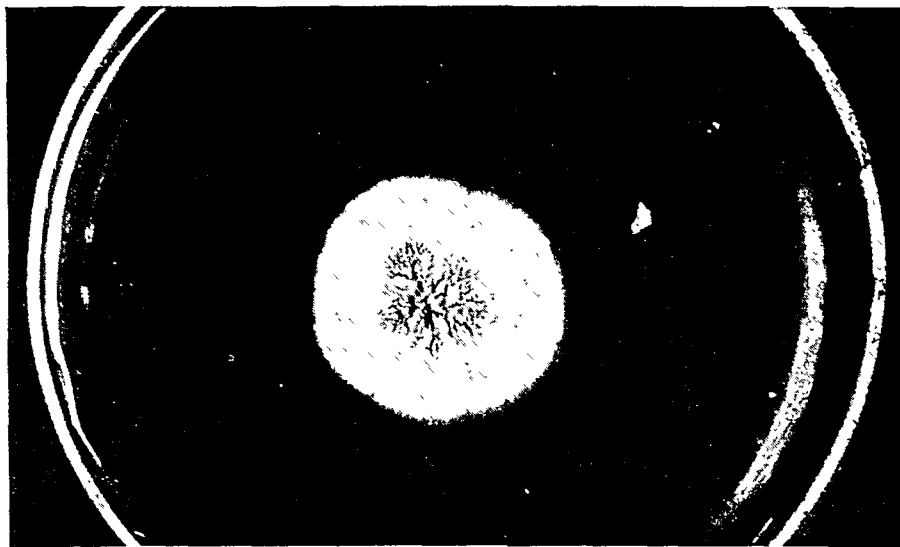


FIG. 3. Colony of *Sporotrichium schenkii*, two weeks old.

developed in 19 out of 20 tubes inoculated with pus. There was practically no bacterial or mold contamination. Growth was noticed on the seventh day after inoculation as a moist, pin-point sized area with a fine fringe. The area slowly increased in size and in two weeks was 2.5 cm. in diameter, was of light brown color and the surface was moist and convoluted. Pigment developed slowly and the growth gradu-

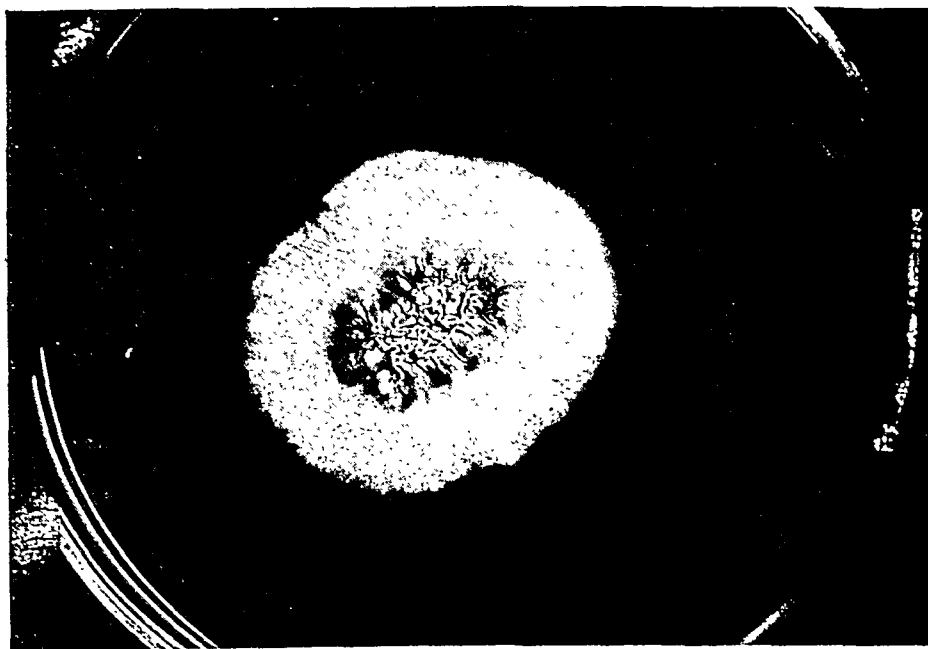


FIG. 4. Colony of *Sporotrichium schenkii* four weeks old. Note the development of pigment.

ally became dark brown. At two months, white excrescences were present on the surface. The young growth had a rubbery consistency tending to friability with increasing age.

Hanging Drop. Hanging drop preparations and specimens made by mixing a small portion of the colony with 15 per cent potassium hydroxide, revealed the grouping of pear-shaped conidia which were present at irregular intervals along the course of hyphae and also appeared as terminal triads and tetrads. Single fructification

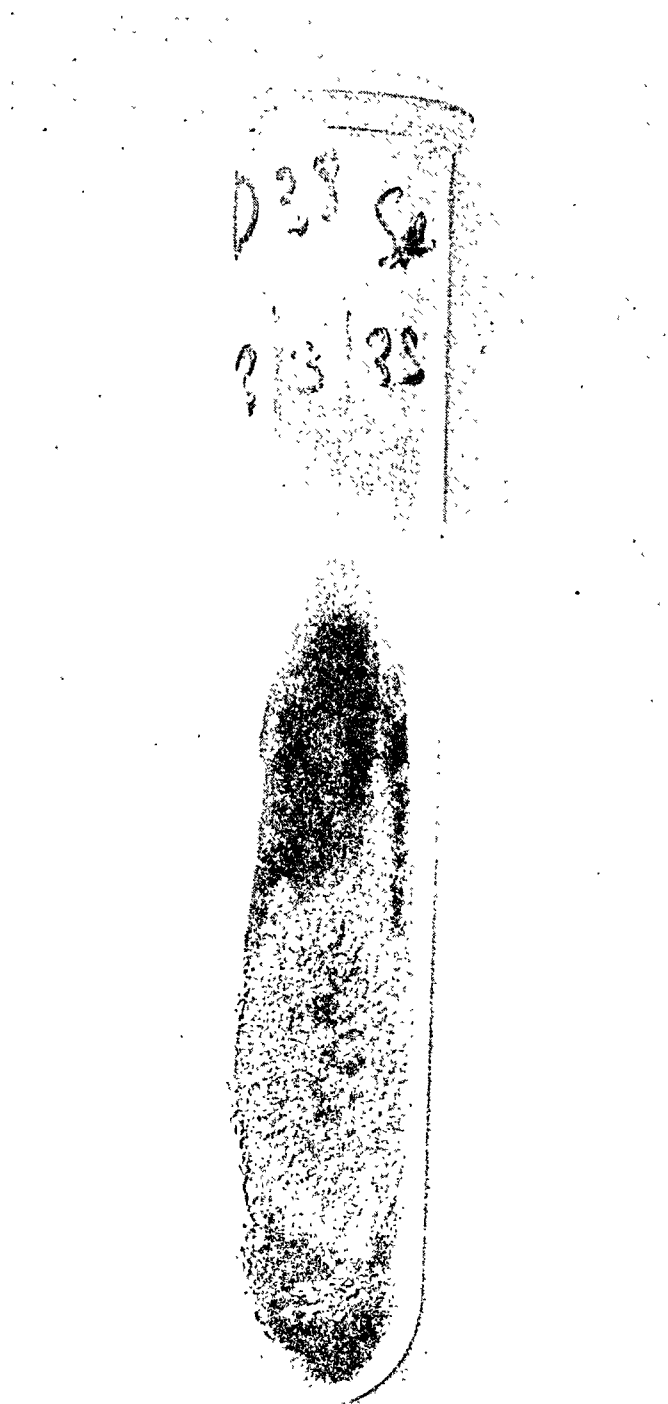


FIG. 5. An older colony of sporotrichium (four months) showing development of white excrescences.

bodies were also observed, attached to the sides of the hyphae. The earlier preparations exhibited a large quantity of fine, branching mycelial threads but in specimens taken from older colonies the picture was dominated by an increased number of spores with very few hyphae in evidence. The diagnosis of *Sporotrichium schenkii* was made.



FIG. 6. Microphotograph of a hanging drop preparation made from sporotrichosis colony, showing branching mycelial threads and the development of groups of pear-shaped spores.

Histological Examination. A small portion of the edge of the initial lesion was excised and examined by Dr. David L. Satenstein. His report follows:

"The epidermis is irregularly acanthotic. The greater part of the cutis is filled with a dense cellular infiltrate. The blood vessels are markedly dilated, some approaching the size of sinuses. Scattered throughout the cellular infiltrate are many very small blood vessels. The cellular infiltrate is composed of a great many mast cells, some connective tissue cells, a few plasma cells and in the central portion there is a large group of giant and epithelioid cells. There are also many polymorphonuclear cells scattered throughout the entire zone. There is no degeneration and no abscess formation. The whole process is one of organizing granulomatous tissue with enormous numbers of mast cells. No fungous elements are noted in routine sections, in those stained by Gram's method or by using polychrome methylene blue."

Animal Inoculation. Studies were made by Dr. A. E. Sheplar, who inoculated

a rat intraperitoneally with a saline suspension of a sporotrichosis colony on February 27. The rat was found dead on May 22. The autopsy revealed a small abscess 5 by 5 mm. between the skin and muscles of the abdomen on the same side as the site of the injection. This was filled with cheesy material. The under surface of the stomach showed several pin-head sized nodules. In the peritoneum of the inoculated side were several small abscesses about 2.5 by 2.5 mm. The testes were greatly enlarged (this enlargement was present for one and one-half months), covered with blood (due to hemorrhage three days previous to death), and filled, when incised, with pockets of pus. The other organs of the body appeared normal.

Culture media implanted with pus developed a growth similar in character to the original colony.

Sections were made from the various organs and reported by Dr. Satenstein as follows:

"Sections of all specimens submitted were stained with hematoxylin eosin, Gram's stain, and polychrome methylene blue. No spores or mycelial threads were demonstrated in any of the sections. The lungs, liver, and kidneys showed some congestion, the last named organ also exhibiting cloudy swelling of the tubules. Considerable granular degeneration was present in the central portion and giant cells were observed at the margin of a lymph node. A nodule near the pancreas consisted of granulomatous tissue composed of giant cell tubercles, surrounded by lymphocytes as well as isolated multinucleated cells. The testes, in the sections examined, showed an inflammatory reaction but no breaking down or abscess formation."

Additional Laboratory Examinations. The Wassermann reaction was negative upon two occasions. The white blood cells were 8,000. The differential count showed: polymorphonuclears 69 per cent, small lymphocytes 28 per cent, large lymphocytes 2 per cent and basophiles 1 per cent. The blood sugar determination was 89.25 mg. per 100 c.c. of blood. No tubercle bacilli were found in the pus, and guinea pig inoculations for tuberculosis were negative. Serum sent to the United States Public Health Service was negative for tularemia and undulant fever.

SOURCE OF THE INFECTION

It is well known that the organism is a frequent saprophyte on many kinds of vegetation. In his comprehensive report and review of the literature, Foerster⁹ found the barberry shrub to be a frequent source of sporotrichotic infection. Benham and Kesten¹⁰ were able to inoculate the organism on carnations causing bud rot. The higher animals are susceptible to the infection and some of the lower animals may also acquire the disease, the rat being particularly vulnerable.

The most common site for the chancre to appear is on the thumb, the index finger and the back of the hand.¹¹ In our patient, the history disclosed the fact that she had transplanted some cactus plants a few days before the initial lesion was first noticed. She wore rubber gloves to protect her hands and since the first lesion developed on skin proximal to that covered by her gloves the cactus plant came under suspicion. We were, however, unsuccessful in proving this point although we inoculated over a hundred tubes of media with several hundred cactus spines. It is interesting to record that cactus plants were growing in the patient's back yard for the past several years. The original source was unknown. Other plants handled were also investigated without any positive result.

TREATMENT

Treatment consisted of:

1. Potassium iodide (saturated solution), beginning with 30 minims daily, and steadily increasing to 90 minims daily. At this dosage symptoms of iodism developed. The dose was decreased to 75 minims and then gradually increased to the point of toleration.

2. Roentgen-ray therapy (one and one-half skin units unfiltered) administered to each lesion.

3. Tincture of iodine applied locally.

At the end of two and a half months all lesions were healed. Iodide therapy was continued for a month longer. There has been no recurrence during the past three months.

SUMMARY

A case of sporotrichosis of the localized lymphangitic type is reported from New York where the disease is of rare occurrence. We were able to find the reports of only three other culturally proved cases originating in this state. The organism was recovered on culture, inoculated successfully in a rat and was identified as *Sporotrichium schenkii*. Treatment by means of iodides and roentgen-rays produced a disappearance of all lesions and there has been no recurrence to date. The source of the infection was not determined.

BIBLIOGRAPHY

1. HOPKINS, J. G., and BENHAM, R. W.: Sporotrichosis in New York State, New York State Jr. Med., 1932, xxxii, 595-601.
2. FOX, H.: Case presentation, Arch. Dermat. and Syph., 1932, v, 531.
3. TURRELL, G. H.: Sporotrichosis, Long Island Med. Jr., 1911, v, 484-488.
4. LAPOWSKY, B.: Sporotrichosis, Jr. Cutan. Dis., 1919, xxxvii, 281.
5. WISE, F.: Case presentation, Arch. Dermat. and Syph., 1921, iv, 268.
6. WALZER, A.: Case presentation, Arch. Dermat. and Syph., 1931, xxiii, 349.
7. MOUNT, L. B.: Sporotrichosis, with report of a rather unusual case, Arch. Dermat. and Syph., 1932, xxv, 528-534.
8. LAWLESS, T. K.: The diagnosis of sporotrichosis, Arch. Dermat. and Syph., 1930, xxii, 381-388.
9. FOERSTER, H. R.: Sporotrichosis, an occupational dermatosis, Jr. Am. Med. Assoc., 1926, lxxxvii, 1605-1609.
10. BENHAM, R. W., and KESTEN, B.: Sporotrichosis; its transmission to plants and animals, Jr. Infect. Dis., 1932, i, 437-458.
11. JACOBSON, H. P.: Fungous diseases: a clinico-mycological text, 1932, Chas. C. Thomas, Springfield, Illinois, p. 132.

THE RELATIONSHIP OF SEX TO DISEASE *

By EDGAR V. ALLEN, M.D., F.A.C.P., *Rochester, Minnesota*

THE RELATIONSHIP of sex to disease is frequently so striking that the lack of major interest in this problem constitutes one of the peculiarities of clinical investigation. Many authors presenting this phase of certain diseases either have simply stated that a difference exists in the incidence by sexes, or have explained the difference with an eye on the disease under consideration, but have neglected the broad problem of the relationship of sex and disease. As a result, the explanations given have been in large part inadequate. Those commonly given for the variation in incidence by sex of disease of the gall-bladder and of cirrhosis of the liver are typical. According to these explanations, pregnancy and obesity cause the greater incidence of disease of the gall-bladder among females, and alcoholism explains the predominance of males among those who have hepatic cirrhosis; yet the ratios of females to males are about the same whether one is considering children or adults.²⁵ Consequently, all the factors given in explanation are valueless, and one's cherished beliefs are shaken.

Early in the course of this study it was apparent that if the surface of the problem were to be more than scratched it would be necessary to examine critically many phases of this interesting relationship. Also, it became obvious that a complete survey of all the aspects of the problem was almost impossible. Such a survey would entail complete examination of all publications dealing with medicine, surgery, pathology and roentgentherapy. All too often the sex of the patient is not stated, terminology varies, and there is reduplication of cases in various reports. Occupation and age influence the distribution of cases according to sex, and these factors are frequently omitted from reports. Even if one could overcome these difficulties, one would find his data of incomplete value. Sex ratio must be corrected by a factor dependent on sex distribution. Unless the ratio of males to females approaches unity in an entire group or population, uncorrected figures of the sex ratio of disease are very misleading. If patients in a given clinic, hospital, or population included twice as many men as women, any disease affecting twice as many men as women would have a corrected ratio of incidence by sex of 1 : 1, whereas uncorrected data would give a ratio of 2 : 1. Hosoi and Alvarez²⁵ have pointed out that more interest in the relationship of sex to disease may stimulate the compilation of better statistical data, but that the obvious inadequacies of the material available handicap any present study. The absence of accurate data should not unduly discourage the investigator. The chief interest lies in the presence of a pattern, manifested by trends or directions of the relationship of sex and disease. My study shows very

* Submitted for publication March 29, 1933.

From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota.

definitely that such a pattern exists which would in all probability be uninfluenced by more trustworthy data.

Data from The Mayo Clinic, which comprise a large part of this study, are subject in part to correction, since the ratio of males to females for a single year (1926) was 1.03:1.²⁵ However, it is apparent that whenever the uncorrected ratios of incidence by sex are not striking, it is quite possible that they are influenced by the various deficiencies indicated.

I have considered in this study only diseases which affect structures common to both sexes. I have further attempted to exclude diseases and structures, such as carcinoma of the breast, which might be influenced by the different physiologic activities of the two sexes, inasmuch as the function of breast tissue of the female and of the male is different. Similarly, adenomatous goiter has not been studied because adenomas tend to occur in colloid goiters, which are more frequent among females.

MORBIDITY

Diseases of the Digestive Tract. The excellent reports by Hosoi and Alvarez, and Günther^{19, 20} facilitate greatly a study of the incidence by sex of gastrointestinal diseases. A glance at figure 1 shows that males are

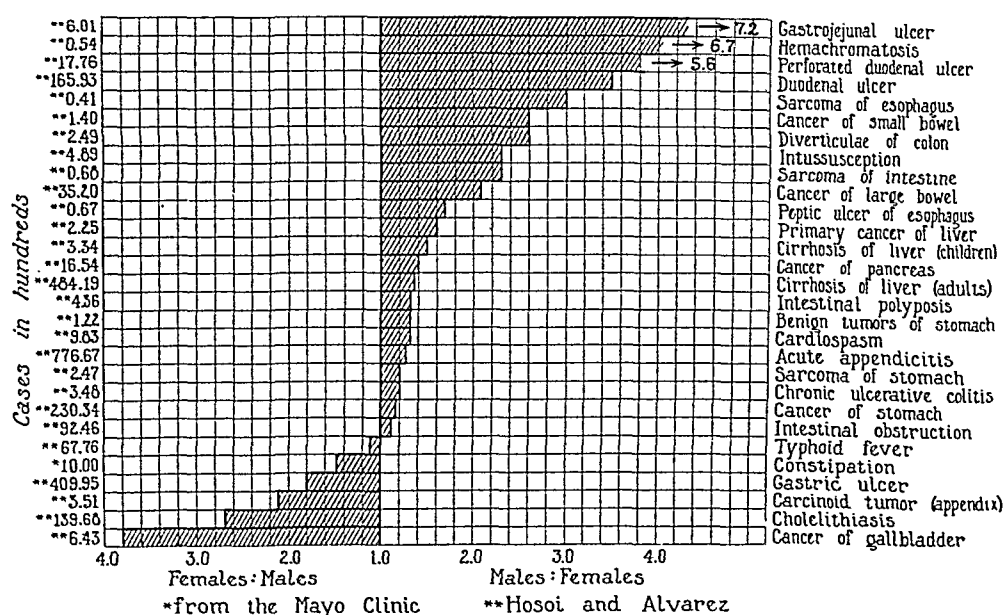


FIG. 1. Diseases of the digestive tract; ratio by sex. Males are preponderantly affected, but cholelithiasis and carcinoma of the gall-bladder are shown to be largely diseases of females.

afflicted with diseases of the digestive tract more than are females. In fact, if gastric ulcer, the incidence of which varies greatly, and constipation, which is really not a disease, were removed from consideration, only carcinoid tumor of the appendix, carcinoma of the gall-bladder, and cholelithiasis remain as diseases affecting the female predominantly. The fact is that the

ratio of males to females, among cases of cholelithiasis, intussusception, and cirrhosis of the liver, is about the same whether one considers children or adults.²⁵ It is interesting that the tendency of a duodenal ulcer to perforate is almost twice as great in the male as in the female. According to Foshee,¹⁴ chronic gastric ulcer occurs in girls and boys in about the same ratio (ten boys : nine girls). The study of Pack and LeFevre³² disclosed a high ratio of males to females among patients who had carcinoma of either the esophagus, stomach, colon, rectum, liver or pancreas; in patients who have carcinoma of the gall-bladder, the ratio of males to females is less than 1 : 1.

Diseases of the Lung and Upper Part of the Respiratory and Digestive Tracts. In figure 2 it is shown that of the diseases of this group which have

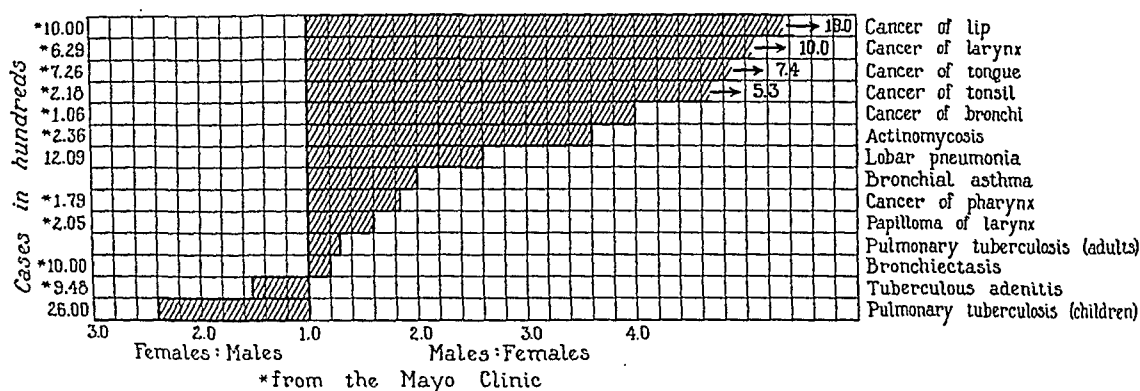


FIG. 2. Diseases of the lung and upper part of the respiratory and digestive tracts; ratio by sex. Only tuberculous adenitis and pulmonary tuberculosis of children affect females more frequently than males.

been studied, only pulmonary tuberculosis in children³¹ and tuberculous adenitis affect females predominantly, whereas bronchiectasis, pulmonary tuberculosis of adults,¹⁰ papilloma of the larynx, carcinoma of the pharynx, bronchial asthma, lobar pneumonia,³⁰ actinomycosis, and carcinoma of the bronchi, the tonsils, the tongue, the larynx and the lip affect males more frequently than females in an ascending degree. The ratio of males to females among patients who have carcinoma of the lip is particularly striking (19.0:1) and that of carcinoma of the larynx (10.0:1) only slightly less so. Pack and LeFevre found similar ratios for carcinoma of the lip, tongue, pharynx, larynx and tonsils, as well as high ratios of males to females for the incidence of carcinoma of the floor of the mouth, buccal mucous membranes, antrum and superior maxilla, inferior alveolus, nasal septum and parotid gland, and for papilloma of the larynx.

Diseases of the Blood, Blood Vessels and Heart. In this group of cases, only varicose veins and chronic mitral endocarditis affect females more frequently than males (figure 3). Considering the former disease, the ratio of females to males is high, probably because of the venous obstruction incident to pregnancy, and because of the great amount of subcutaneous fat which furnishes poor supporting tissue in the female. The high comparative incidence of valvular heart disease among females may be due to their greater

susceptibility to chronic arthritis, although such a condition is not commonly associated with valvular heart disease. The cases of chronic adhesive pericarditis are from the report of Smith and Willis,³⁶ who selected the cases on the basis of records of postmortem examination. The high ratios of

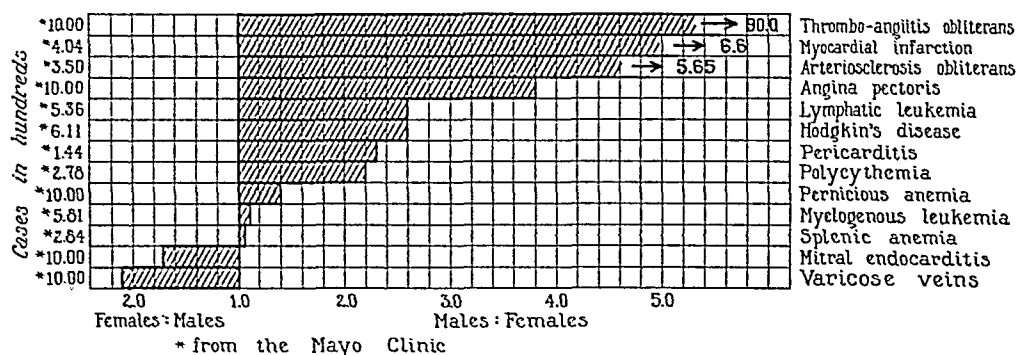


FIG. 3. Diseases of the blood, blood vessels and heart; ratio by sex. The high incidence of diseases of the peripheral arteries and heart among males is striking. The term arteriosclerosis obliterans is used to denote sclerosis and occlusion of the peripheral arteries.

males to females in the incidence of thromboangiitis obliterans, myocardial infarction, occlusive arteriosclerotic disease affecting the extremities, angina pectoris, lymphatic leukemia, Hodgkin's disease, and polycythemia are striking. Günther²¹ has expressed the belief that diseases of the arteries occur more frequently among men, whereas diseases of the veins occur more frequently among women.

Although syphilis is not, strictly speaking, a disease of the blood, it is convenient to consider it under this heading. An excellent report of the incidence by sex of this disease has been given by Turner,⁴⁰ who studied 10,000 cases, in 5,017 of which the patients were males and in 4,983, females. His figures for syphilitic meningitis, syphilis of the skin and mucous membranes (taken together), cardiovascular syphilis, syphilis of the central nervous system, general paresis and tabes dorsalis show that the ratio of males to females is 2.0:1, 1.0:1, 2.8:1, 2.2:1, 3.0:1, and 4.9:1 respectively. Syphilis affects the skeletal system of males more commonly than that of females. The ratio of females to males for latent syphilis is 1.7:1.

The greater immunity of the female to syphilis has been the subject of a treatise by Warthin,⁴¹ who has reviewed the possible causes of such comparative immunity. He felt that perhaps: "The *Spirocheta pallidum* is a pathogenic descent of some harmless spirochetel form inhabiting the female body ages ago, and in consequence woman establishes a more comfortable partnership with this organism than does man." Pregnancy also appears to influence favorably the course of a syphilitic infection. However important these explanations are, the fact remains that most other diseases also affect men more commonly. The explanation is probably valid in all instances and constitutes one which I shall consider more in detail later.

Diseases of the Bones, Joints and Urinary Tract. Of this group of dis-

eases only chronic infectious arthritis* and nonstructural backache affect women more frequently than men (figure 4). The latter disease may occur

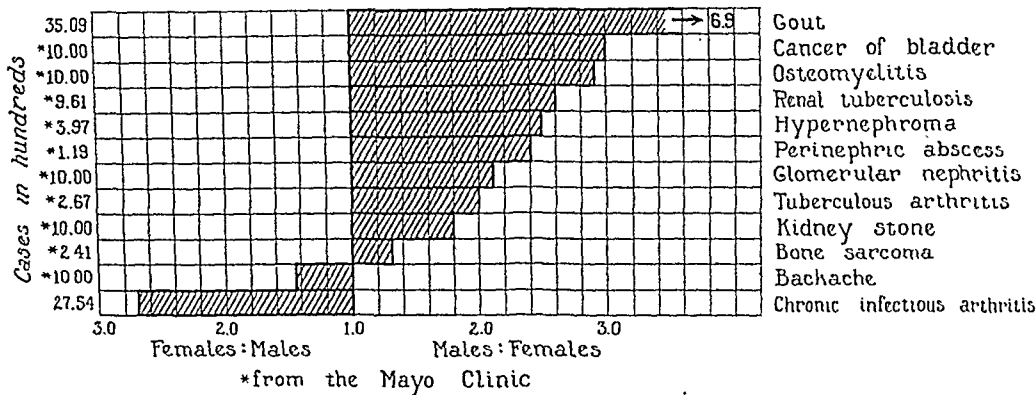


FIG. 4. Diseases of the bones, joints and urinary tract; ratio by sex.

among women more commonly, because it may be a manifestation of nervousness and chronic fatigue, or because of pathologic or abnormal physiologic conditions concerning the female organs of reproduction. The incidence of malignancy involving the osseous and urinary tracts is greater among males, as is the incidence of carcinoma elsewhere in the body. Pack and LeFevre found the following respective ratios of males to females for papilloma of the bladder, carcinoma of the bladder and hypernephroma: 2.0: 1, 3.4: 1 and 2.0: 1. Although the incidence of pulmonary tuberculosis among adults is greater in males than in females (figure 2), the difference in incidence for the two sexes is less than that seen in renal tuberculosis. The figures on gout are those of Hench,²² who collected 3,509 cases from the literature. Hench believes the ratio given in figure 4 is much too low, for the diagnosis as applied to females was frequently erroneous. The ratio for cases observed by him was 40.0 males to 1 female. Ehrström¹³ gave for gout, a ratio of males to females of 20.0: 1.

Miscellaneous Diseases. The ratios for most of the diseases in this group (figure 5) are not striking. Obesity, pityriasis rosea, and urticaria

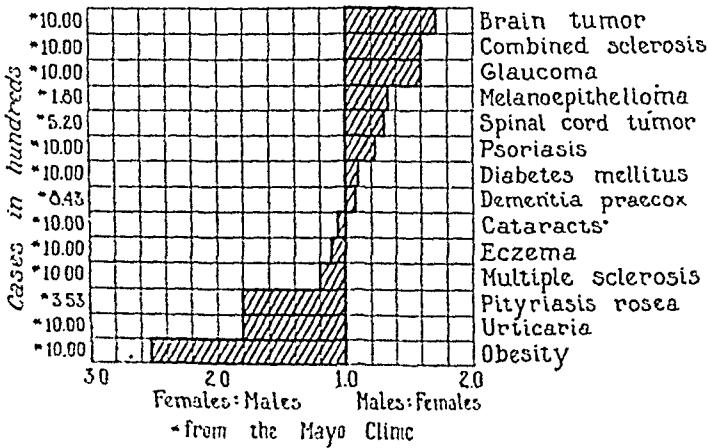


FIG. 5. Miscellaneous diseases; ratio by sex.

* Data from the American Committee for the control of rheumatism.

affect females more commonly than males. Tumor of the brain, combined sclerosis of the posterior and lateral columns of the spinal cord, and glaucoma, are predominantly diseases of males. The high ratio of combined sclerosis is due in part to the greater incidence of pernicious anemia (figure 3) among males. Obesity may affect females more frequently because of their more sedentary life, and because of their frequently abnormally large appetite in pregnancy. Pack and LeFevre have shown that adenomatous goiter affecting males is more likely to become carcinoma than when affecting females. Breitner and Just³ found that carcinoma develops among 3.8 per cent of females and 5.8 per cent of males who have nodular goiters.

Functional Nervous Diseases. This is the single group of diseases in which females are affected more frequently than males (figure 6). Some

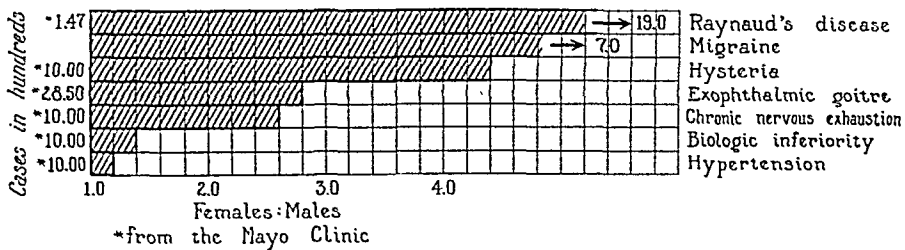


FIG. 6. Functional nervous diseases; ratio by sex. All of the diseases studied have a higher incidence for females than for males. Therefore, there is no space in the figure representing diseases which affect males predominantly.

objection may be raised to the inclusion of Raynaud's disease, exophthalmic goiter, and hypertension in this group of cases. However, Allen and Brown¹ have indicated the functional nature of Raynaud's disease; exophthalmic goiter appears to be a manifestation of imbalance of the sympathetic nervous system, and essential hypertension in its early stages is definitely an evidence of disturbance of the sympathetic nervous system. The factors explaining the predominance of exophthalmic goiter among females have been discussed by Gardiner-Hill.²³ Riseman and Weiss,³⁵ in a review of the ratio by sexes in hypertension, found figures greatly at variance. In their series, 30 per cent were males. Draper¹² stated that of patients who have migraine, the ratio of females to males is 7.0:1; among 1,000 cases seen at The Mayo Clinic, it was only 2.1:1. An interesting side light on the incidence of nervous disturbances by sexes was furnished by Gaupp,¹⁶ who noted that four men committed suicide to each woman, although women made more suicidal attempts ("nicht ernste gemeinte!"). The distribution of diseases of the nervous system by sex has been furnished by Günther.¹⁵

Comment. The study, thus far, has dealt with morbidity, and it appears that the male is less favorably situated as far as most of the diseases under consideration are concerned. However, I have been dealing with a highly selected group of diseases, such as would bring the patients long distances to large medical centers. A survey of all the illnesses in a community, or among large numbers of people under observation, might give entirely

different results. Sydenstricker³⁷ has shown, in such a study, that the male ratio of sickness is consistently less than that of the female. The records of Leipzig Local Sick Fund for the period of 1887 to 1905, covering the illnesses of 259,582 females and 952,674 males, show that the incidence of sickness among females was definitely greater than that among males up to the age of 55 years, after which the reverse was true.³⁷ Similar results were found in a study by the Metropolitan Life Insurance Company, dealing with 376,573 persons, except that the incidence of sickness among females was found to exceed that among males only up to the age of 45 years.³⁷ Sydenstricker's study of the children of Hagerstown, Maryland, disclosed that the incidence of most diseases among children under five years of age was higher among boys than among girls, but that in adolescence there was a higher incidence among girls for all diseases for which comparisons are warranted.³⁸ Collins, who studied 5,071 school children, found that the incidence of sickness was consistently higher for girls than for boys.⁹ Britten found that rates of physical impairment are on an average higher for women than for men.⁴ The figures of 935 German Krankenkassen for 1930 are at variance with those just given. Among the 2,500,000 members there were 45.8 cases of illness for each 100 men, and only 40.7 cases for each 100 women.²⁶ These are insurance figures, difficult of evaluation because of the influence which sick benefits have on the number of claims of illness, and inasmuch as they contradict the experiences of other investigators, are probably influenced by peculiar circumstances. Britten's study of the influenza epidemic revealed inferior resistance of the male.⁵ The incidence of influenza was distinctly greater among females, but the mortality was higher among males.

The available data, then, indicate that females are sick more than males. However, my study shows that among males there is a higher incidence of most diseases which might permanently influence health or endanger life.

MORTALITY

It occurred to me that if the conclusion just reached was entirely justified, the predominant morbidity ought to have a well marked influence on the mortality rates. The sources of my studies on mortality were the reports of the United States Bureau of Census and the United States Mortality Statistics.^{15, 29} I have used the compiled data of 1920 in both instances, for no census report has been published since this date. It is obvious that the mortality figures for the same year must be used in order to secure the ratio of deaths to the entire population. The mortality among males is higher than that among females with the exception of persons aged 20 to 34 years, inclusive, when the death rate among females is higher, apparently due to the mortality from childbirth.* The ratio of males to females (deaths of males

* Senior Statistician Britten of the United States Public Health Service has pointed out to me that the increased mortality for females in the age group mentioned was true in 1920 but not true in 1900, 1910 or 1930.

for each 100,000 males/deaths of females for each 100,000 females) is shown in figure 7, and indicates the increased mortality for males in all periods of life except during the inclusive ages of 20 to 34 years.

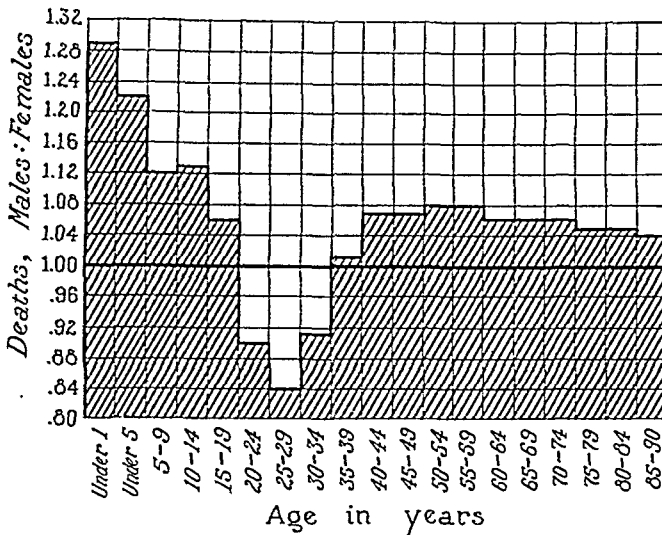


FIG. 7. Ratio of deaths of males among each 100,000 males to deaths of females among each 100,000 females in the registration area of the United States for 1920. The mortality for males is more than one in all age groups with the exception of the inclusive ages of 20 to 34 years. The calculation by which the ratio was obtained is explained in the text.

Further evidence of the higher mortality among men is the expectancy of shorter life for them. Wiehl's⁴² figures for 1927 show that at the age of 10 years females can expect 55.32 years of life, and males only 51.88 years. According to this author, the expectancy for life of persons who reach maturity actually decreased between the years of 1921 to 1927, due to the greater mortality among men. Wiehl also showed that mortality begins earlier in life for men than for women. Bakwin² has shown that the decrease in infant mortality has been greater for females than for males.

Since the rate of death among males is higher than that among females, the ratio of males to females in the entire population ought to show a resulting shift. Actually this is the case. Males outnumber females in the total population at all ages up to 20 years, when the female population is greater. The difference, although slight, persists during the ages of 25 to 29 years inclusive, when the number of males again exceeds that of females, with a rough parallelism occurring until the age of 55 years. At this point there is a gradually diminishing predominance of males in the population of the United States, until, at the age of 75 years, the females outnumber the males and continue to do so. Therefore, when the age of 100 years is reached, there are almost twice as many females as males.

This study now allows several conclusions. It appears that females are sick oftener but less seriously than males; but that most serious diseases are contracted by a higher proportion of males; that the rate of mortality is uni-

formly higher for males than for females, with the exception of the age period of from 20 to 34 years inclusive; that this increased mortality influences the entire population, so that the ratio of females to males in the registration area of the United States gradually increases from the age of 55 years onward, and that the expectancy of males at the age of 10 years is less than that of females by about three and a half years.

The factors which are usually set down in explanation of the greater mortality of males are overwork, alcoholism, venery, tobaccoism, exposure to the elements, industrial hazards, and irregular habits of eating and sleeping. It occurred to me that the validity of such an assumption could be tested by selecting patients who were subject to none of these factors. Consequently I have studied (1) intra-uterine mortality; (2) congenital deformities, and (3) mortality in the early years of extra-uterine life.

Intra-Uterine Mortality. Holmes and Mentzer²⁴ have shown that from 103 to 108 males are born for each 100 females, depending on the population studied. The mortality rates for males during intra-uterine life is consistently predominant, varying with the different months after conception, from 375 to 118 males for each 100 females. These are important figures, having to do with a group of persons far removed from the influences usually advanced as explanations of the greater rate of mortality among males. Here are data so striking as to seem erroneous were it not for the fact that they fit so easily into the pattern which is beginning to form. Here is evidence that the male is fundamentally the weakling of the two sexes.

To digress from the subject of mortality for a moment: Congenital deformities are tremendously predominant among males. The ratios (male to female) for congenital pyloric stenosis, Meckel's diverticulum, Hirschsprung's disease, esophageal diverticulum, harelip, cleft palate and renal agenesis⁸ are 3.9:1, 3.7:1, 3.3:1, 2.1:1, 1.6:1, 1.5:1 and 1.2:1, respectively. Here again are astonishing data, the validity of which can be tested by a study of mortality in the early years of life.

Mortality in the Early Years of Life. In the registration area of the United States in 1920, 8,500 males and 6,700 females died for each 100,000 males and for each 100,000 females, respectively, of that part of the total population which is less than one year of age. The corresponding figures for that part of the population less than five years of age were 2,300 and 1,900, respectively. The ratio of males to females (deaths of males per 100,000 males/deaths of females per 100,000 females) for that part of the population less than one year of age was 1.29:1 and for the population less than five years of age it was 1.21:1 (figure 7). The data for infants less than one year of age are excellent for comparison, inasmuch as both girls and boys lead their existence largely in a crib; boys receive diets no different from girls, and both are equally protected from extraneous factors which might influence mortality. Yet the corrected ratio of mortality for boys to girls is 1.29:1. The lives of boys and girls who are less than five years of

age are practically identical, aside from the fact that boys are possibly more subject to trauma by virtue of their greater activity, and are more exposed to infectious disease because of their wider contacts. Yet these factors, if they are present, influence the mortality of males favorably rather than unfavorably, for the corrected ratio of mortality for boys to girls is 1.21:1; less therefore than that for infants less than one year of age.

GENERAL COMMENT

The present study indicates that serious disease involving structures common to both sexes afflicts males oftener than females. That this is not due to some habit or habits of life peculiar to the male is indicated by the greater male mortality rate during intra-uterine life, and for the first five years of extra-uterine life, as well as by the predominance of congenital deformities among males.

The mechanism and cause of this inherent weakness of the male are difficult to explain. Clarke⁷ felt that inasmuch as males are larger than females at birth, intra-uterine nutrition would be more difficult and birth injury would be more common; and that latent effects of unrecognized birth injury might account for the difference in mortality later. One might predicate that a wise Nature, knowing males to be numerically less important in the scheme of reproduction, is less careful of them, but it is strange that she should allow them to be conceived in superabundance, only to begin immediately to reduce their number by death.

There is considerable evidence that the male is more highly differentiated from the neuter or species type than is the female.^{27, 34} Castration of the male produces far more extensive effects than does castration of the female. Furthermore, the castrated male takes on characteristics which are in many respects similar to those of the female. The gist of this hypothesis is that the male, representing advanced or more specialized development, is more susceptible to disease, in the same way that all organisms having highly specialized tissues are more susceptible to derangement than are simple unicellular organisms.

The metabolism of males, according to Draper, is 2 to 4 per cent higher than that of females. This difference is illustrated by the fact that whereas the egg is large, quiescent, and stores up energy, the sperm is small, active, and spends energy. Geddes and Thompson¹⁷ have felt that femaleness is characterized by preponderant anabolism and maleness by preponderant catabolism. This increased catabolic tendency of the male might well influence his resistance to disease. Whatever the explanation for the influence of sex on disease may be, it appears incontrovertible that there exists a sex-linked inferiority of the male; that mere maleness influences unfavorably the resistance of the organism to disease during all ages.

One might object to the hypothesis that susceptibility to disease is determined along with sex^{11, 28, 33} only to be held quiescent for the many years be-

tween conception and the appearance of the disease; yet examples are common in medicine. An inherited tendency to baldness, hypertension, abnormal arteriosclerosis, and even brevity of life or longevity, may remain unrecognized for years, only to come into view at a period of life which careful study of family records would have allowed one to predict.

For each explanation of the lack of inherent vitality of the male there are objections, but these do not influence the fact; the male is, by comparison with the female, a weakling at all periods of life from conception to death. Venery, alcoholism, exposure, overwork, and various other factors may influence the susceptibility to disease and the greater mortality of the adult male, but they are only straws placed on the greater burden of his sex-linked weakness. There seems to be no doubt that, speaking comparatively, the price of maleness is weakness. How ironical therefore seems the precept of the apostle (I Peter: I, 13): "Give honor unto the wife as unto the weaker vessel."

The possible facts brought out by this study are worthy of further investigation. The results of various therapeutic endeavors need to be carefully studied from the standpoint of how they are influenced by sex. W. J. Mayo has stressed the comparative seriousness of certain diseases when they affect males instead of females. More studies of the differences in physiologic and chemical processes of the two sexes are urgently needed,^{6, 30} and there is a crying need for better medical statistics. Only in these ways can the full effect of sex on disease be adequately investigated. Finally, the therapeutic implications should not be overlooked. Hemophilia, purely a disease of the male, usually can be adequately controlled by ovarian therapy. The use of preparations of organs which determine the sex characteristics of the female may, in the future, be found of value in the treatment of thromboangiitis obliterans, angina pectoris, gout and arteriosclerosis, while the sex glands of the male given therapeutically to the female may favorably influence Raynaud's disease, migraine, and functional nervous disturbances.

Certainly this interesting phase of medicine has been too much neglected. It is to be hoped that the future will witness gratifying progress in the study and understanding of the fascinating problem of the relationship of sex to disease.

REFERENCES

1. ALLEN, E. V., and BROWN, G. E.: Raynaud's disease: clinical study of 147 cases, Jr. *Am. Med. Assoc.*, 1932, xcix, 1472-1478.
2. BAKWIN, H.: Sex factor in infant mortality, *Human Biol.*, 1929, i, 90-116.
3. BREITNER, B., and JUST, E.: Quoted by PACK and LEFEVRE.
4. BRITTEN, R. H.: Sex differences in the physical impairments of adult life; comparison of rates among men and women, based on 112,618 medical examinations by the Life Extension Institute, *Am. Jr. Hyg.*, 1931, xiii, 741-770.
5. BRITTEN, R. H.: The incidence of epidemic influenza, 1918-1919; further analysis according to age, sex, and color of records of morbidity and mortality obtained in surveys of 12 localities, *Pub. Health Rep.*, 1932, xlvii, 303-339.

6. CHARLES, E.: Comparative studies of sex differences in calcium and magnesium content of serum, *Quart. Jr. Exper. Physiol.*, 1931, xxi, 81-91.
7. CLARKE, J.: Observations on some causes of the excess of the mortality of males above that of females, *Phil. Trans. Roy. Soc. London*, 1786, xvi, 122-130.
8. COLLINS, D. C.: Congenital unilateral renal agenesis, *Proc. Staff Meetings of Mayo Clinic*, 1931, vi, 581-584.
9. COLLINS, S. D.: Morbidity among school children in Hagerstown, Maryland, *Pub. Health Rep.*, 1924, xxxix, 2391-2422.
10. CORNET, G.: Tuberculosis and acute general miliary tuberculosis; *In: NOTHNAGEL'S Encyclopedia of Practical Medicine*, 1904, W. B. Saunders Company, Philadelphia.
11. DAVENPORT, C. B.: Inheritance in poultry, 1906, Carnegie Institute, Washington.
12. DRAPER, G.: The influence of sex upon the constitutional factor in disease, *New York State Jr. Med.*, 1925, xxv, 1065-1070.
13. EHRSTRÖM, R.: The sex as a factor in pathogenesis of disease, (Abstr.) *Jr. Am. Med. Assoc.*, 1921, lxxvi, 1288.
14. FOSHEE, J. C.: Chronic gastric ulcer in children; report of case, *Jr. Am. Med. Assoc.*, 1932, xcix, 1336-1339.
15. Fourteenth Census of the United States 1920 Population, 1922, ii, Government Printing Office, Washington.
16. GAUPP, R.: Über die Geschlechtsunterschiede bei Psychosen und ihre Bedeutung für eine vergleichende Psychologie der Geschlechter, *Ztschr. f. Sexual-wissensch.*, 1929, xvi, 81-87.
17. GEDDES, P., and THOMPSON, J. A.: Quoted by DRAPER.
18. GÜNTHER, H.: Die Bedeutung der Sexualdisposition bei Erkrankungen des Nervensystems, *Deutsch. Ztschr. f. Nervenh.*, 1926, xc, 1-37.
19. GÜNTHER, H.: Über die Geschlechtsunterschiede bei Krankheiten der Verdauungsorgane, I. Krankheitsdisposition, *Arch. f. Verdauungskr.*, 1927, xl, 83-115.
20. GÜNTHER, H.: Über die Geschlechtsunterschiede bei Krankheiten der Verdauungsorgane; II. Krankheitsverlauf, *Arch. f. Verdauungskr.*, 1927, xl, 159-173.
21. GÜNTHER, H.: Die Bedeutung der Sexualdisposition in der Pathologie des Blutgefäßsystems, *Ztschr. f. Kreislaufforsch.*, 1929, xxi, 217-238.
22. HENCH, P. S.: Personal communication to the author.
23. GARDINER-HILL, H.: Etiological study of primary Graves' disease, with special reference to significance of sex events of female, *Quart. Jr. Med.*, 1929, xxii, 217-236.
24. HOLMES, S. J., and MENTZER, V. P.: Changes in sex ratio in infant mortality according to age, *Human Biol.*, 1931, iii, 560-575.
25. HOSOI, K., and ALVAREZ, W. C.: The influence of sex on the incidence of gastrointestinal disease, *Human Biol.*, 1930, ii, 63-98.
26. *Journal American Medical Association Correspondence: Relative incidence of sickness among men and women*, *Jr. Am. Med. Assoc.*, 1932, xcix, 487.
27. LAURENT, E.: Quoted by DRAPER.
28. MORGAN, T. H.: *Heredity and sex*, 1913, Columbia University Press, New York.
29. *Mortality Statistics, twenty-first annual report, 1920. 1922*, Government Printing Office, Washington.
30. NORRIS, G. W., and LANDIS, H. R. M.: *Diseases of the chest and the principles of physical diagnosis*, Ed. 4, 1929, W. B. Saunders Company, Philadelphia.
31. OPIE, E. L., LANDIS, H. R. M., MCPHEDRAN, F. M., and HETHERINGTON, H. W.: Tuberculosis in public school children, *Am. Rev. Tuberc.*, 1929, xx, 413-420.
32. PACK, G. T., and LEFEVRE, R. G.: Age and sex distribution and incidence of neoplastic diseases at the Memorial Hospital, New York City, with comment on "cancer ages," *Jr. Cancer Res.*, 1930, xiv, 167-294.
33. PEARL, R.: Quoted by DRAPER.
34. POLLAILON: Quoted by DRAPER.

35. RISEMAN, J. E. F., and WEISS, S.: Age and sex incidence of arterial hypertension, *Am. Heart Jr.*, 1929, v, 172-190.
36. SMITH, H. L., and WILLIUS, F. A.: Correlation of clinical and pathologic features of adherent pericarditis, *Proc. Staff Meetings of Mayo Clinic*, 1931, vi, 697-698.
37. SYDENSTRICKER, E.: Illness rate among males and females; Hagerstown morbidity studies, *Pub. Health Rep.*, 1927, xlii, 1939-1957.
38. SYDENSTRICKER, E.: Sex differences in the incidence of certain diseases at different ages; Hagerstown morbidity studies, *Pub. Health Rep.*, 1928, xliii, 1259-1276.
39. TSURUTA, T.: Relation of sex to susceptibility to toxicity of bile salts, *Med. Bull. Univ. Cincinnati*, 1931, vii, 134-136.
40. TURNER, T. B.: Race and sex distribution of lesions of syphilis in 10,000 cases, *Bull. Johns Hopkins Hosp.*, 1930, xlv, 159-184.
41. WARTHIN, A. S.: Sex differences in pathologic picture of syphilis (Joseph Price lecture), *Am. Jr. Syphilis*, 1928, xii, 301-315.
42. WIEHL, D. G.: Some recent changes in mortality among adults, *Jr. Preventive Med.*, 1930, iv, 215-237.

center, progressive sterilization of the meninges, with some recoveries, could be produced.

Kolmer found it difficult to duplicate this treatment in human beings because here treatment is frequently delayed to the point at which the subarachnoid fluid is extremely purulent and accompanied by plastic exudate. He recommends the use of antipneumococcus serum to every 25 c.c. of which has been added 1 c.c. of 1 per cent optochin solution. Felton's serum is preferable because of its high content of antibodies. Kolmer advised that the serum-optochin mixture be injected into the cisternal space, after drainage, and that it also be injected into the carotid arteries.

CASE REPORT

A. S., white female, age 20, fell while dancing December 31, 1932, striking her head on the floor. A slight swelling appeared on the left forehead but no other signs developed until the afternoon of the following day (January 1, 1933) when she complained of a severe headache.

Her past history was irrelevant except for frontal and maxillary sinusitis in the winter and spring of 1931-1932.

She was first seen January 2, 1933 by one of us (N. McL.). Her temperature was 101°. The headache was persistent; there was tenderness over the right maxillary antrum and ethmoid area, and the right ear drum appeared to be bulging. The following day (January 3) the temperature was unchanged, the headache was of increased severity, and she complained of some disturbance in vision. The condition continued unchanged until the evening of January 5 when she had two severe chills and became increasingly stuporous. On the morning of January 6 the tenderness noted before over the right maxillary antrum and ethmoid region had shifted to the left side and there was a noticeable bulging of the left eyeball. Examination for evidence of sinus involvement was made at this time by Dr. J. W. Croushore and none was found. The patient continued to develop increased visual disturbance, stupor, and headache. Her temperature mounted to 102°. Vomiting developed. She was transferred to the hospital January 7, 1933.

Examination on admission showed a well developed young white female, somewhat disoriented and stuporous, whose temperature was 103.4° and pulse 70. The blood pressure was 130 systolic and 80 diastolic. There was a marked bulging of the left eye, a choking of the inner half of the left optic disc, slight nasal congestion, rigidity of the neck and back, sluggish knee reflexes, a negative Babinski and a positive Kernig sign.

These findings, together with the history, warranted a diagnosis of meningitis. Spinal puncture was performed. There was no increased pressure and the fluid was slightly opalescent. The laboratory findings are recorded in table 1.

She was given 25 c.c. of 50 per cent glucose solution intravenously every six hours, and an additional effort was made to reduce cerebral pressure by means of rectal instillations of 33 per cent magnesium sulphate solution.

January 8: Patient was somewhat brighter. Temperature 102°, pulse 74. The physical findings were unchanged. The headache was still severe. The rectal instillations of magnesium sulphate were discontinued. Chloral hydrate in 15 grain doses was given for restlessness. Intravenous injections of 25 c.c. of 50 per cent glucose solution every six hours were continued, and a 5 c.c. ampule of 5 per cent Uritone solution was given intravenously every four hours. By late afternoon she was irrational, there was slight cyanosis, the temperature was 104.4°, and the pulse 96. There was a slight bloody discharge from her nose containing an occasional clot of blood.

TABLE I
Laboratory Findings

	Cerebrospinal Fluid						Blood Count						Treatment
	Cell Count	Glob- ulin	Smear	Sugar	Gold Curve	Culture	Total White Cells	Fila- ment	Non- Fila- ment	Small Lymph- ocyte	Endo- thelials		
Jan. 7	3530	4 +	Not made	—	0002333300	Bile soluble encapsulated diplococci (Pneumococci Types I and II)	12700	49%	26%	22%	3%	Symptomatic	
Jan. 9	4860	4 +	Polynuclears and pneumococci	—		"	13900	48	24	24	4	30000 units Felton's serum (intravenously)	
Jan. 10	1400	2 +	"	—		"	23300	58	30	8	4	10000 units intravenously	
Jan. 11	5800	3 +	"	—		"	12900	55	19	21	5	10000 units intraspinally	
Jan. 12	950	3 +	"	—		"	25400	56	28	8	8	10000 units intravenously	
Jan. 13	(Cistern fluid) Not counted	4 +	"	—		"	20000	54	30	10	6	20000 units intravenously	
Jan. 14	2320	4 +	"	—		"	17500	60	25	12	3	20000 units intracranially	
Jan. 15	320	2 +	"	—		"	15500	66	18	13	1	10000 units intravenously	
Jan. 16	(Cistern fluid)			.061 gm.			15200	67	17	16	0	10000 units intravenously	
Jan. 17	1150	3 +	Polynuclears— No organisms	+	0012332100	No growth	14500	62	18	18	2	No serum	
Jan. 18												"	
Jan. 19	870	2 +	"	.058 gm.		Pneumococci	11000	67	14	18	1	"	
Jan. 20							13000	63	16	20	1	"	
Jan. 21							13400	60	16	22	2	"	
Jan. 22												"	
Jan. 23	860	2 +	Polynuclears— No organisms	.048 gm.		Occasional pneumococci	12500	57	15	26	2	"	
Jan. 24												"	
Jan. 25							11000	57	15	25	3	"	
Jan. 26							14000	57	16	25	2	"	
Jan. 27	90	4 +	Polynuclears and pneumococci	.070 gm.		Occasional pneumococci	12500	60	15	22	3	"	
Jan. 28							11500	60	15	23	2	"	
Jan. 29							9800	58	14	25	3	"	
Jan. 30							9500	58	14	26	2	"	
Jan. 31							10000	60	16	22	3	"	
Feb. 1	50	4 +	Polynuclears— No organisms	.065 gm.	1222334321	No growth	9200	60	15	22	3	"	
Feb. 2												"	
Feb. 3												"	
Feb. 4	40	2 +	Few polynuclears No organisms	.062 gm.		No growth	10000	60	13	23	4	"	

Blood culture Jan. 7 and Jan. 9 showed no growth.

This epistaxis became more marked during the night so that it was necessary to pack the nose.

January 9: Temperature 101.8°, pulse 72. The headache was severe, and the patient was somewhat irrational. Her left eye was still prominent and slight internal strabismus was noted. Rigidity of the neck was marked. The abdominal reflexes were hyperactive, the knee reflexes sluggish, the Kernig sign was positive and the Babinski negative.

Spinal puncture showed the fluid cloudy and under increased pressure (34 mm. mercury). There was no evidence of subarachnoid block. Twenty cubic centimeters were withdrawn. The culture of the spinal fluid withdrawn on January 7 showed pneumococci. On typing, these were found to agglutinate with Type I and II sera.

The use of Felton's antipneumococcic serum was believed indicated, and after preliminary tests for serum sensitivity, 10,000 units were given intravenously at 11 a.m., 3:30 p.m., and 7:45 p.m. All other treatment was discontinued.

January 10: Temperature 101.2°, pulse 82. The patient's condition was essentially unchanged. The internal strabismus of the left eye was more marked. Edema of the nasal portion of left optic disc was still pronounced. Spinal tap showed cloudy fluid under increased pressure. Queckenstedt's sign was negative. Ten thousand units of Felton's serum were instilled intraspinally by gravity. At 2:30 p.m. 10,000 units of Felton's serum were given intravenously. She felt somewhat improved late that afternoon but by evening she was quite irrational. A drawing downward of the right corner of the mouth was noted.

January 11: During the night difficulty in swallowing developed. At 4:30 a.m. the temperature was down to 99.8° and the pulse 80. Her condition seemed improved in the morning. The headache was better. Strabismus of the left eye was still marked. Right facial paralysis with inability to purse the lips and contract the orbicularis oculi muscle was quite pronounced. She was given 10,000 units of serum intravenously. In the afternoon she began to complain of more headache. The temperature rose to 103° but the pulse for the first time was up to 108.

January 12: Patient had urinary retention during the night and required catheterization in the morning.

Temperature 102.4°, pulse 100. Blood pressure 124/74.

Spinal puncture was performed: the pressure was up to 30 mm. mercury. Queckenstedt's sign was negative. Fifteen cubic centimeters of cloudy fluid were withdrawn (pressure reduced to 8 mm.). Ten thousand units of Felton's serum were given intravenously at 10 a.m. and again at 6 p.m.

January 13: Comfortable night. Temperature 101.4°, pulse 88.

Cisterna puncture was performed and 20 c.c. of cloudy fluid withdrawn and 20,000 units of Felton's serum instilled. This was followed by dyspnea which was relieved by seven minims of adrenalin hydrochloride (1-1000) and $\frac{1}{4}$ gr. of morphine.

January 14: Temperature 99.8°, pulse 100. Spinal puncture was performed and 20 c.c. of cloudy, thick, yellowish, rapidly coagulating fluid were withdrawn. Queckenstedt's sign was negative. The cell count could not be done. Ten thousand units of Felton's serum were given intravenously immediately following the spinal tap. The patient had a comfortable day.

January 15: Temperature 100.2°, pulse 100. Definite general improvement was noted. The headache was practically gone. Soreness and stiffness of the neck and back were still marked. The strabismus of the left eye and protrusion of the eyeball were practically completely gone. The edema of the left optic disc had cleared. The abdominal reflexes were hyperactive, the knee reflexes sluggish, and the Babinski negative. Kernig's sign was negative on the left but positive on the right.

Spinal puncture performed: pressure not increased; Queckenstedt's sign negative; fluid yellow and opalescent. Ten thousand units of Felton's serum were given intravenously.

January 16: Temperature 99.8°, pulse 92. The patient was very comfortable. The reflexes showed the same responses as on the previous day.

Spinal tap was attempted both in the fourth and third lumbar interspaces but was unsuccessful. Cisterna puncture was performed and 25 c.c. of clear fluid withdrawn. Because of the freedom from symptoms, and in view of the cisterna fluid findings and the drop in the non-filament percentage from 25 to 18 (table 1), no serum was given. From this day on, the non-filament percentage of polynuclear cells, in addition to the cerebrospinal fluid findings, was used as a guide in deciding the necessity for further serum treatment.

January 17: Temperature 101.8°, pulse 110. A slight increase in the activity of the knee reflexes was noted. The right Kernig was only slightly positive. Slight improvement in the right facial paralysis was observed. The patient's condition seemed satisfactory and she was quite comfortable. No spinal tap was performed and no serum given.

January 18: Temperature 99.6°. The patient had a very comfortable day. The knee reflexes were active, the Kernig sign negative. The facial paralysis was unchanged.

Spinal puncture showed opalescent fluid under normal pressure. Queckenstedt's sign was negative. No serum was given.

January 19: During the night the temperature rose to 103°. In the morning the patient showed an urticarial rash over the legs, thighs, arms and chest. For the first time there was noted a paralysis of the external rectus muscle of the right eye with inability to move the eyeball laterally beyond the midline.

Spinal tap showed an opalescent fluid under no increased pressure.

January 20 and 21: Condition remained unchanged. The urticaria began to clear up but joint pains were quite marked. Salicylates were administered.

January 22: The patient developed a mild coryza and occipital headache. Her condition was otherwise good.

January 23: The patient's condition was satisfactory although there was still a slight temperature rise. The abdominal reflexes were normal as were the knee reflexes. The Kernig and Babinski signs were negative. The right facial paralysis showed slight improvement but the abducens paralysis remained unchanged.

Spinal tap showed turbid fluid under no increased pressure.

January 24, 25, 26: The patient's condition showed steady improvement.

January 27: Facial and abducens paralysis improved. Spinal fluid clear, yellowish, and under normal pressure.

January 28, 29, 30, 31: Condition good. Facial and abducens paralysis improving slowly.

February 1: Condition good. Spinal fluid clear, pressure not increased.

February 4: Spinal fluid clear. Pressure not increased.

She was discharged from the hospital on February 5, 1933. Her physical condition was good. The facial paralysis was clearing rapidly but the right abducens paralysis was improving only very slowly.

By April 1 her facial paralysis had cleared up completely. The right abducens paralysis also showed evidence of improvement, but this was not progressing as rapidly.

Eye examination by Dr. Parker Heath on April 4, 1933 showed vision 5/6 in both eyes; measurement of muscle balance showed 14 degrees esophoria for distance and the same in accommodation.

The ophthalmoscopic examination showed some loss of transparency along the course of the vessels, otherwise the findings were normal.

Visual field studies showed nothing significant. There were no scotomata and the blind spots were normal. There was residual squint in the right eye.

On April 3, 1933 stereoscopic roentgen-ray studies were made of the skull by

Dr. Edward G. Minor. There was no evidence of any definite sinus pathology nor of any recent or old fracture.

SUMMARY

1. A patient with pneumococcic meningitis (probable portal of entry the paranasal sinuses), with the infecting organism pneumococcus Type I and II, was successfully treated by intravenous, intraspinal and intracisternal instillations of 120,000 units of Felton's anti-pneumococcic serum.

2. Recovery set in after seven days of treatment and was evidenced not only by clinical improvement but by a reappearance of sugar in the cerebrospinal fluid, a lowering of its cell count, and a drop in the percentage of non-filament cells in the blood smear. This latter finding, namely the non-filament percentage,¹⁹ was relied upon as a gauge of the activity of the infection. As long as this figure remained between 8 and 16 it was felt that the infectious process was under adequate control.

3. As a residuum of the disease, the patient had a right facial and a right abducens paralysis. The former developed on the fourth day and the latter on the day after admission to the hospital. The facial involvement cleared rapidly but the sixth nerve paralysis took fully two months longer for recovery.

BIBLIOGRAPHY

1. Quoted by KENNEDY, W. R.: Pneumococcic meningitis, Canadian Med. Assoc. Jr., 1928, xix, 336-339.
2. ROBERTSON, O. H.: Two cases of meningitis due to pneumococcus Type III, Med. Clin. N. Am., 1929, xiii, 375-380.
3. HARKAVY, J.: Pneumococcus meningitis; recovery with serum therapy, Jr. Am. Med. Assoc., 1928, xc, 597-599.
4. ROHRBACH, H. O.: Pneumococcic meningitis with recovery, Penna. Med. Jr., 1929, xxxii, 646-647.
5. Quoted by CARBONELL and COOK.¹⁴
6. APFEL, H.: Pneumococcic meningitis treated with Pregl's solution; recovery; report of case, Arch. Pediat., 1929, xlv, 516-520.
7. LYNCH, L. J.: Pneumococcus meningitis with recovery, New Eng. Jr. Med., 1930, cciii, 256-257.
8. SIMPSON, A. S.: Case of pneumococcal meningitis, with complete recovery following serum treatment, Lancet, 1927, i, 390-391.
9. SHULLER, E. H.: Pneumococcic meningitis; case report, with one recovery, Jr. Oklahoma State Med. Assoc., 1932, xxv, 137-140.
10. CROFT, C. R.: Case of pneumococcal meningitis, with recovery, Lancet, 1928, ii, 700-701.
11. UHR, J. S.: Pneumococcus meningitis; report of case in new-born infant, with recovery, Arch. Pediat., 1929, xlv, 121-123.
12. GLOBUS, J. H., and KASANIN, J. I.: Pneumococcus (Type IV) meningitis; report of case treated by forced subarachnoid drainage, with recovery, Jr. Am. Med. Assoc., 1928, xc, 599-601.
13. AMESSE, J. W.: Pneumococcic meningitis; report of case with recovery, Colorado Med., 1931, xxviii, 361-362.
14. CARBONELL, A., and COOK, E. L.: Pneumococcus meningitis; report of a case treated with ethylhydrocuprein and Huntton's antibody solution, with recovery, Mil. Surg., 1928, lxiii, 718-723.

15. Quoted by CARBONELL and COOK.¹⁴
16. WEINBERG, M. H.: Case of pneumococcus (Type III) meningitis treated with potassium permanganate—recovery; plea for its trial, *Jr. Nerv. and Ment. Dis.*, 1931, lxxiv, 38-45.
17. STEWART, F. W.: Local specific therapy of experimental pneumococcal meningitis; incidental myelitis, abscess, and organization of exudates, *Jr. Exper. Med.*, 1928, xlvii, 1-7.
18. KOLMER, J. A.: Newer methods for prophylaxis and treatment of meningitis with special reference to streptococcus and pneumococcus meningitis, *Laryngoscope*, 1932, xlii, 12-33.
19. FARLEY, D. L., ST. CLAIR, H., and REISINGER, J. A.: Normal filament and nonfilament polymorphonuclear neutrophile count; its practical value as diagnostic aid, *Am. Jr. Med. Sci.*, 1930, clxxx, 336-344.
- MULLIN, W. V., and LARGE, G. C.: Filament-nonfilament count; its diagnostic and prognostic value, *Jr. Am. Med. Assoc.*, 1931, xcvii, 1133-1139.
- REVENO, W. S., and BERENT, M. S.: Routine use of filament-nonfilament count, *Jr. Mich. State Med. Soc.*, 1932, xxxi, 443-449.

CHICAGO AS A MEDICAL CENTER

FROM a mere stockade with two blockhouses established as Fort Dearborn in 1803 by the United States Government, Chicago has had a noteworthy development. The many phases of Chicago's phenomenal growth from an insignificant hamlet of log houses to a metropolitan center of great importance were dramatically portrayed at A Century of Progress from June to November of 1933.

Of all the exhibits at the World's Fair, none drew more close observation and widespread acclaim than those dealing with medicine, surgery, and the basic and allied sciences, most of which were located in the Hall of Science. In concise form these exhibits showed the lay public what medicine has accomplished during the last 100 years, and how Chicago has contributed to that development.

While the purpose of this article is to call the attention of physicians to the Chicago of today as a medical center, a brief word as to the development of medicine in Chicago may be in place.

Medical Schools. Early medical needs were met by the Army surgeons and a few pioneer general practitioners. An important step was taken when in 1837 Daniel Brainard, a cultured, well educated man—he had studied in Paris—who was already a leading surgeon in the Northwest, founded Rush Medical College. Dr. Brainard gathered about him a notable group of men and from 1837 to the present time Rush Medical has been a prominent school in Chicago and the Northwest. Its long association with the Presbyterian Hospital and the Central Free Dispensary and its affiliation and later union with the University of Chicago, its voluntary raising of standards, its four year course, its compulsory fifth year are among the epochs in its history and help explain its leadership in medicine, its production of notable practitioners and specialists of many types and its contributions to medical science and literature.

In Dr. Brainard's faculty for several years was a young man, N. S. Davis. It has well been said that two men of the type of Daniel Brainard and N. S. Davis, each determined to lead and unable to follow, could not be members of the same faculty. So N. S. Davis, taking with him such men as William H. Byford, H. A. Johnson and Daniel Rutter, left Rush Medical College and founded the Chicago Medical College. This school was to demand higher entrance requirements and to have a graded course. Whether Dr. Brainard did not believe in the principle of these changes or in the feasibility of putting them into practice at that time is not quite clear, but Dr. Davis did believe in the principle and did put them into practice. Later all colleges followed his lead. From its first course in 1859 to the present, the Chicago Medical College has had a career of progress and today, as Northwestern University Medical School with magnificent labora-

tory and clinical buildings, a superior faculty and an enthusiastic student body, it is well known in the medical field.

The College of Physicians and Surgeons, a proprietary medical school, was started in 1881, depending largely on the nearby Cook County Hospital for its clinical advantages. It had many outstanding didactic and laboratory teachers and did good work. In 1897 it became the Medical Department of the University of Illinois. It still has the advantage of being located in "the medical center of the west side," close to the Cook County Hospital, but it now has splendid modern buildings of its own, embracing



FIG. 1. Rush Medical College.

hospitals, research departments, out-patient department and library. It is a university of which the state is justly proud.

Many small second or third rate medical schools sprang up in Chicago in the last 30 or 40 years of the nineteenth century. Several of these died a natural death. Others were given a lethal potion by the American Medical Association through its Council on Medical Education. Several schools were gathered into the Medical Department of Loyola University. This latter institution immediately began re-arranging, improving the physical plants, unifying work, raising standards, until today it is a Class A school

in high favor, with a good faculty and a worthy group of teaching hospitals under its control—Mercy, Misericordia, St. Anne's, St. Bernard's, St. Elizabeth, St. Mary of Nazareth, John B. Murphy, Alexian Brothers, Lewis Memorial and Oak Park.

Following out the plan of President William R. Harper, the University of Chicago for some years confined its medical course to the work given in the Departments of Anatomy, Pharmacology, Pathology, Bacteriology, Physiology and Chemistry. For the last few years, however, it has given a full four year medical course on the University campus. A fine group

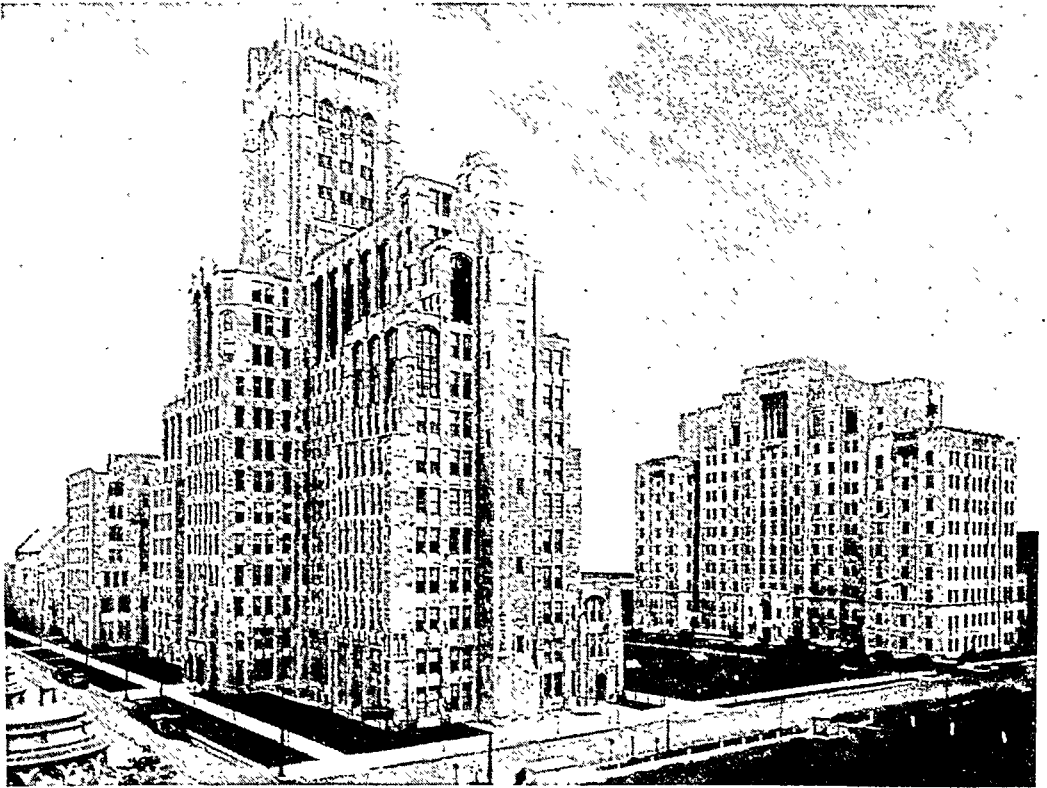


FIG. 2. Montgomery Ward Memorial Building of Northwestern University Medical School, with Passavant Hospital in the background.

of buildings was erected, largely through the efforts of Dr. Frank Billings. While research is stressed, undergraduate teaching is also carried out. The students at the end of the first two years choose whether they will remain at the University on the south side to continue work or will go to the west side to Rush Medical College. All students on finishing their four years are eligible for the degree of doctor of medicine conferred by the University of Chicago.

To these different medical schools and to their hospitals, laboratories, research departments and wards, the College of Physicians will be invited to demonstrations and clinical conferences that will surely be informing and

stimulating. It will also be of interest to many members to see the physical plants of some of the departments, and the equipment, and to learn the methods of teaching and investigation that are there in vogue.

Hospitals. There are in Chicago more than 100 hospitals. Of these, in 1933, 62 were on the approved list of the American College of Surgeons. Discussion of these hospitals will be confined to those which will participate most actively in the meeting of the American College of Physicians.

Cook County Hospital is a tax-supported institution maintained for the medical and surgical treatment of the indigent poor. It was founded on March 30, 1847. The City Hospital, opened in 1856, was purchased

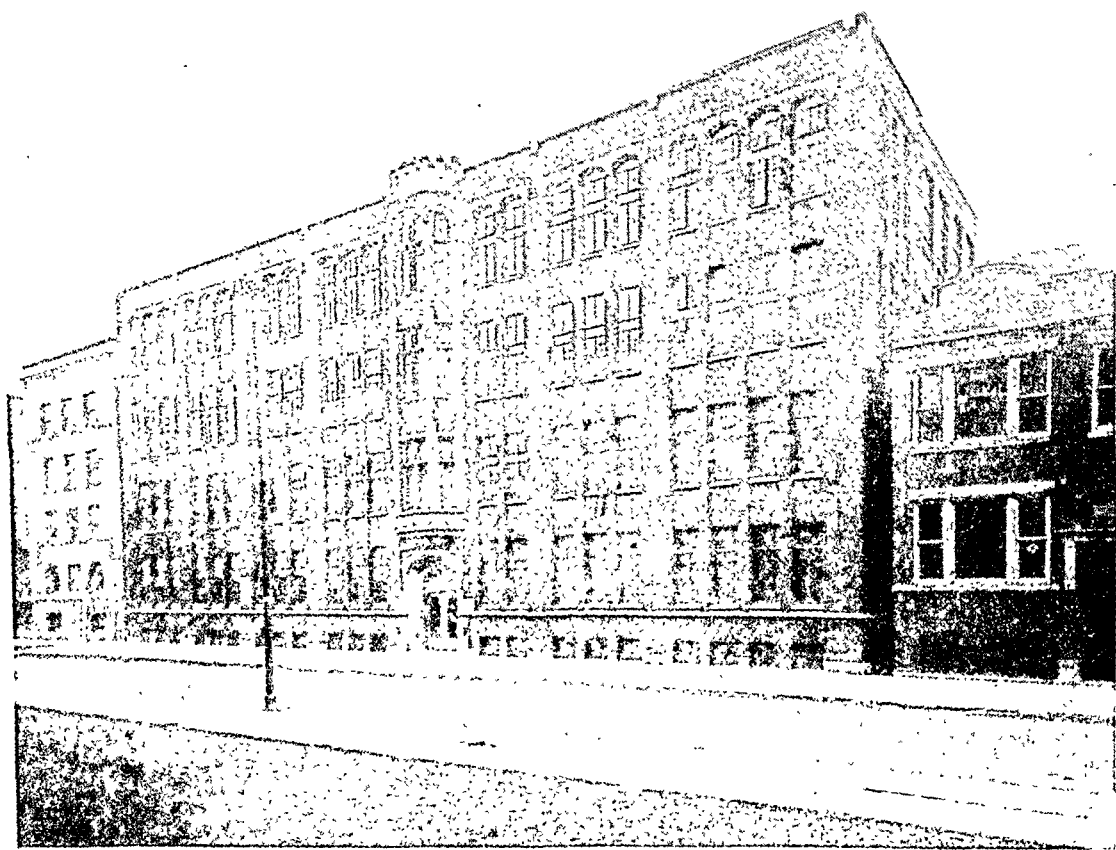


FIG. 3. Loyola University School of Medicine.

by Cook County in 1866. Between the years 1863 and 1865 it had been used as a United States military hospital.

In figure 4 are shown the seven buildings comprising the Cook County Hospital which is situated in the medical center of Chicago. The divisions of Cook County Hospital are: general, children, psychopathic, laboratory, tuberculosis, men's medical, and contagious. The hospital has a capacity of 3300 beds. The attending staff consists of 130 physicians who serve for a period of six years and are under Civil Service. There are 93 interns at present who serve an internship of 18 months each. In addition there are 33 residents.

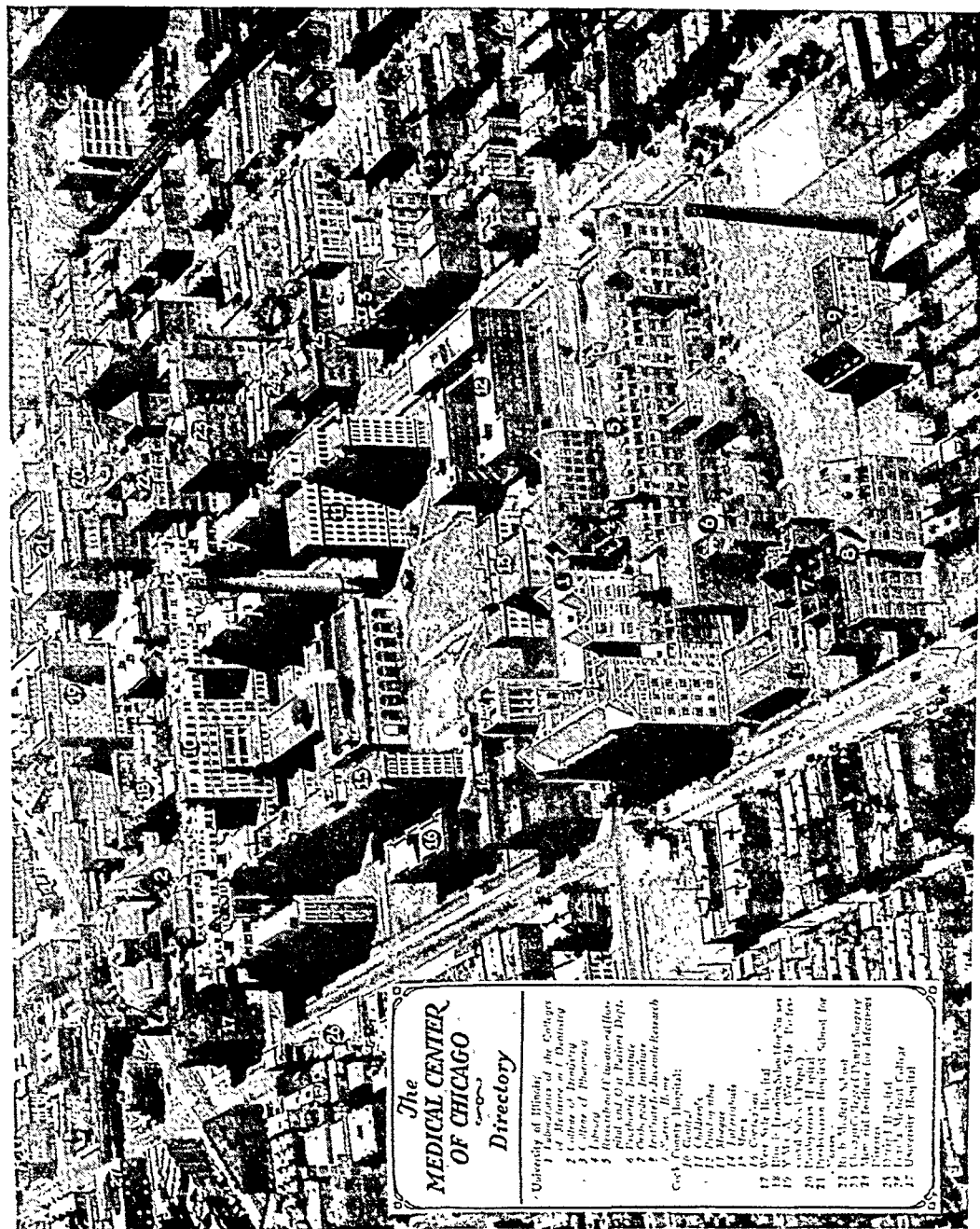


FIG. 4. Airplane view of the medical center of Chicago.

The MEDICAL CENTER OF CHICAGO

Directory

- 1 University of Illinois
 2 Laboratories of the College
 3 Department of Pathology
 4 Culture of Bacteria
 5 Culture of Phages
 6 Library
 7 Research and Development
 8 Department of Pathology
 9 Department of Pathology
 10 Department of Pathology
 11 Department of Pathology
 12 Department of Pathology
 13 Department of Pathology
 14 Department of Pathology
 15 Department of Pathology
 16 Department of Pathology
 17 Department of Pathology
 18 Department of Pathology
 19 Department of Pathology
 20 Department of Pathology
 21 Department of Pathology
 22 Department of Pathology
 23 Department of Pathology
 24 Department of Pathology
 25 Department of Pathology
 26 Department of Pathology
 27 Department of Pathology

It is impossible to estimate the enormous influence the County Hospital has had on the medical work of Chicago. Though often harmfully enmeshed in politics, though at times operating in an atmosphere of extravagance, mismanagement and graft, it has gone ahead caring for—and in general well caring for—an increasing number of the indigent sick through its attending and intern staff. The positions on each one of these staffs have always been coveted, not so much for the prestige attached to them as for the opportunity to increase clinical experience. The roll of the names on the attending staff includes along with forgotten political appointees a goodly proportion of the city's leading physicians, surgeons and specialists, with many teachers of outstanding ability. The list of ex-interns, whose appointment for years has been on the basis of competitive examination, is an impressive one, including names well known not only in Chicago and the United States but often abroad as well. In this list—we omit the names of those still living—we find among others Nicholas Senn, William E. Quine, E. Fletcher Ingals, Roswell Park, William T. Belfield, John B. Murphy, Frank Billings, John A. Fordyce, S. P. Black, Weller Van Hook, A. E. Halstead, Adolph Gehrmann, H. T. Ricketts, and Theodore Ticken.

There has always been carried out in Cook County Hospital some type of undergraduate instruction in amphitheater, morgue, ward or laboratory. This is true today. A recent development is the organization, not for profit, of the Cook County Graduate School of Medicine. Started in 1932, this school will, through the hospital staff, utilize the wealth of facilities afforded by the hospital. Short courses of a few weeks or longer ones of a year will be offered in clinics, wards, laboratories of various kinds, the out-patient department, morgue, etc. The fact that in the first year of its existence 250 physicians were enrolled seems to indicate that the school is meeting a demand and that it bids fair to prosper.

Another public institution deserving of mention is the Municipal Tuberculosis Sanitarium. This was opened in 1915 and is a specialized hospital with services for all stages of pulmonary tuberculosis. It has a capacity of 1246 beds. Its wards are open for teaching to the various medical schools of the county.

Mercy Hospital (figure 5) is one of the oldest hospitals in Chicago, having been started in 1849 as the Illinois General Hospital of the Lakes. Under the management of the Sisters of Mercy it has grown to be a general hospital of 365 beds, caring for all types of disease except contagious. Its institute of radiation therapy, containing some of the finest roentgen-ray facilities in the United States, places Mercy in a position to treat any type of tumor or malignant disease. Its ample teaching facilities are utilized by Loyola University with which it is intimately related. Without disparagement of others, one may say there are three names which by common consent are associated with the development of Mercy Hospital, N. S. Davis, Sister Raphael, and John B. Murphy. Each one of these gave years of devoted

service to the upbuilding of the institution to the end that it might better take care of patients and spread medical knowledge through instruction in its wards and amphitheaters.

Plans for St. Luke's Hospital were consummated during the Civil War. A hospital to care for the sick soldiers of Camp Douglas was very much needed. As a result a frame building with a seven bed capacity was opened in 1864. Today St. Luke's—by the way the tallest hospital in the world—has a bed capacity of 659 with investment in land, buildings and equipment of more than \$5,000,000. On its staff are many of the leading practitioners of Chicago. Its intern service is eagerly sought. Small clinics and ward clinics are open to undergraduates. Excellent work has been and is being

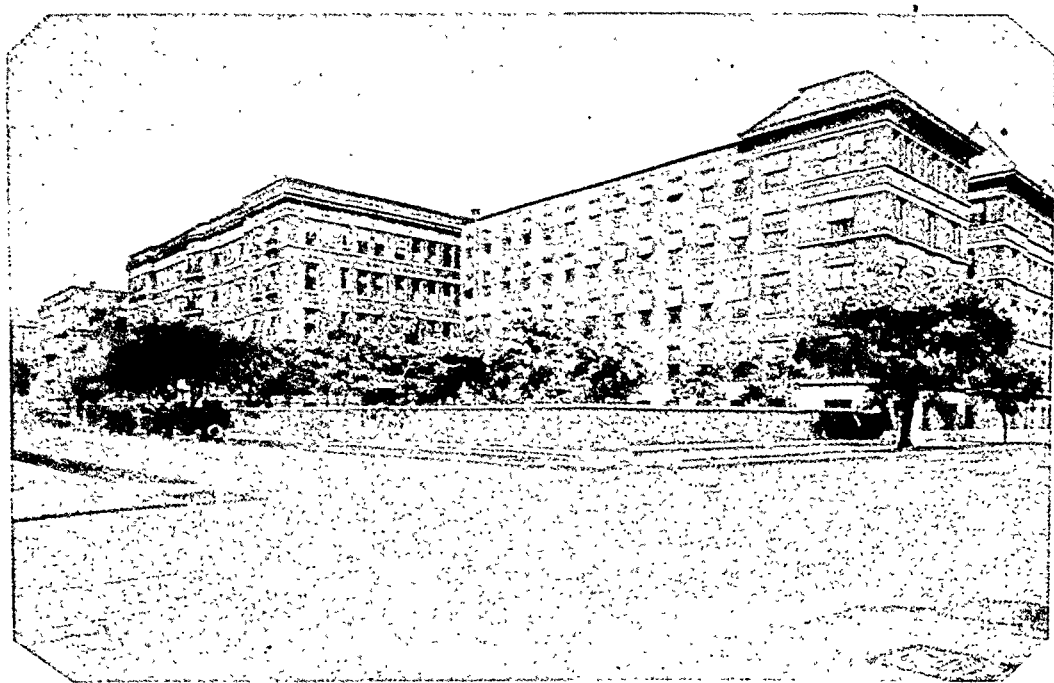


FIG. 5. Mercy Hospital.

done in roentgen-ray, pathological and other laboratories. The school of nursing is of highest rank.

Michael Reese Hospital grew out of the first Jewish hospital established in Chicago, in 1868. This hospital was destroyed by the fire of 1871. Michael Reese, who died in 1873, left through his will a fund sufficient to erect a new building. The United Hebrew Charities of Chicago founded the institution, named it in honor of Michael Reese and made it non-sectarian. In the last few years, largely through special funds given by various donors, there has been a remarkable development of research work at Michael Reese, and various interesting clinical and laboratory investigations are now being carried on. Among the special departments of the hospital may be mentioned the cancer clinic, the radium therapy, electro-

therapy and cardiac departments, the prenatal station and the department of pediatrics. The out-patient department, social service department and nursing school are all of high grade.

Passavant Memorial Hospital (figure 2) was established in 1865, being at that time called the Deaconess Hospital. It was located in a frame residence with a capacity of only 15 beds. When the founder, the Rev. William A. Passavant, died in 1894 the name was changed. In 1926 the new Passavant Memorial Hospital was constructed on the downtown campus of Northwestern University. It has a capacity of about 250 beds; and its equipment for the treatment of patients is of the most modern type. It is

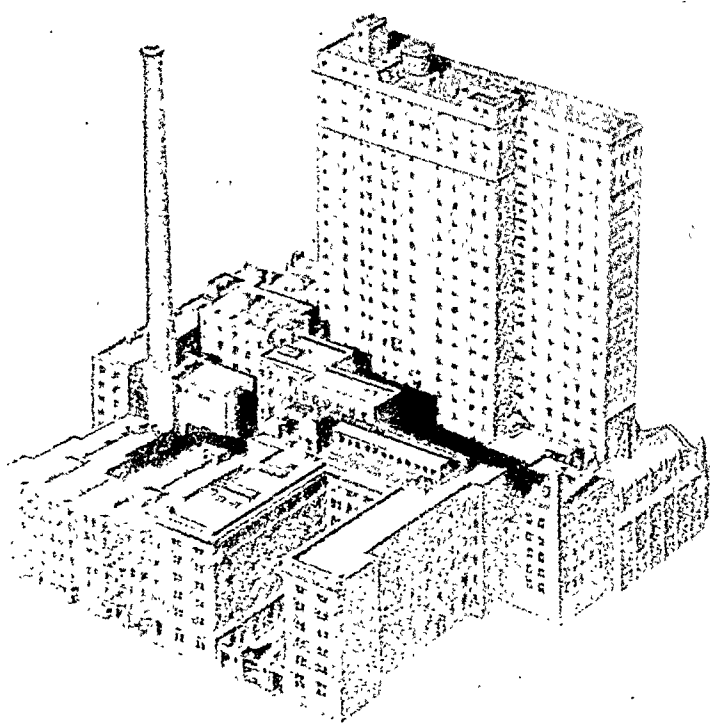


FIG. 6. St. Luke's Hospital.

controlled in its medical management by Northwestern University and is well utilized as a teaching and research hospital by that University.

It may be mentioned here that Wesley Hospital, founded in 1888 and a beneficiary of funds left by William Deering, is another hospital affiliated with Northwestern University. Its wards are used for teaching. It is planned that ultimately it will be on the same campus with Northwestern University Medical School.

Presbyterian Hospital was founded in 1883 by Dr. Joseph P. Ross, a member of the faculty of Rush Medical College, largely because he felt the need of a teaching hospital to care for the clinic patients of Rush. From a small beginning it has gradually enlarged until now it has 439 beds and, together with the building of Rush Medical College, occupies an entire block.

Its close association with the College, which controls its staff appointments, and with the Central Free Dispensary, and of late its affiliation with the University of Chicago have made it a center of teaching and research. Its wards are open to undergraduate students. Its training school is justly famed.

The Research and Educational Hospitals (figure 9) had their origin on July 5, 1919 when the State Department of Public Welfare and the State University agreed upon a plan for constructing and maintaining a group of hospitals, laboratories, library and allied institutions in the medical center of Chicago on the West Side. Their aim was to provide medical treatment for

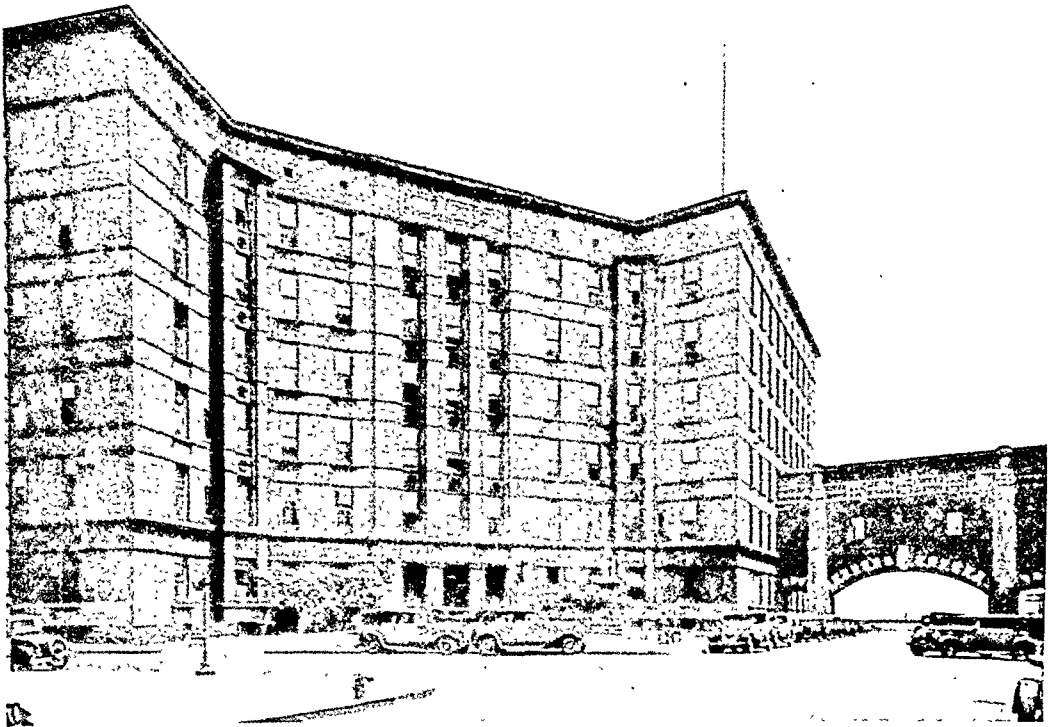


FIG. 7. Michael Reese Hospital.

the indigent sick of the state, to educate practitioners in the prevention as well as the cure of disease and to foster research. Not all the hospitals and laboratories planned have been constructed, but a splendid beginning has been made. The clinical building for the medical department has been put up. In September 1924 the out-patient department of the Research and Educational Hospitals was established. The general hospital was opened in 1925. The Surgical Institute for Children was opened in the spring of 1930, and in 1931 the Psychiatric Institute started receiving patients.

The University of Chicago Clinics comprise a group of hospital and medical buildings situated for the most part on the University campus. The English Gothic style which is characteristic of all the University buildings

has been carried out very successfully in the architecture of the medical group. In addition to the service rendered to the public by the care of a large number of patients, the purpose of the clinics is to afford exceptional opportunities to students of medicine who are preparing for a career as practitioners, teachers or investigators. In all departments stress is laid upon research, and valuable studies are everywhere in progress.

The Albert Merritt Billings Hospital, a unit of the University of Chicago Clinic, was opened in 1927 as a general hospital and has also been used for gynecology and orthopedic surgery. It includes an out-patient department, the Max Epstein Clinic. The pediatric department is housed in the Bobs Roberts Memorial Hospital for Children. The Nancy Adele McElwee Memorial and the Gertrude Dunn Hicks Memorial, together with the

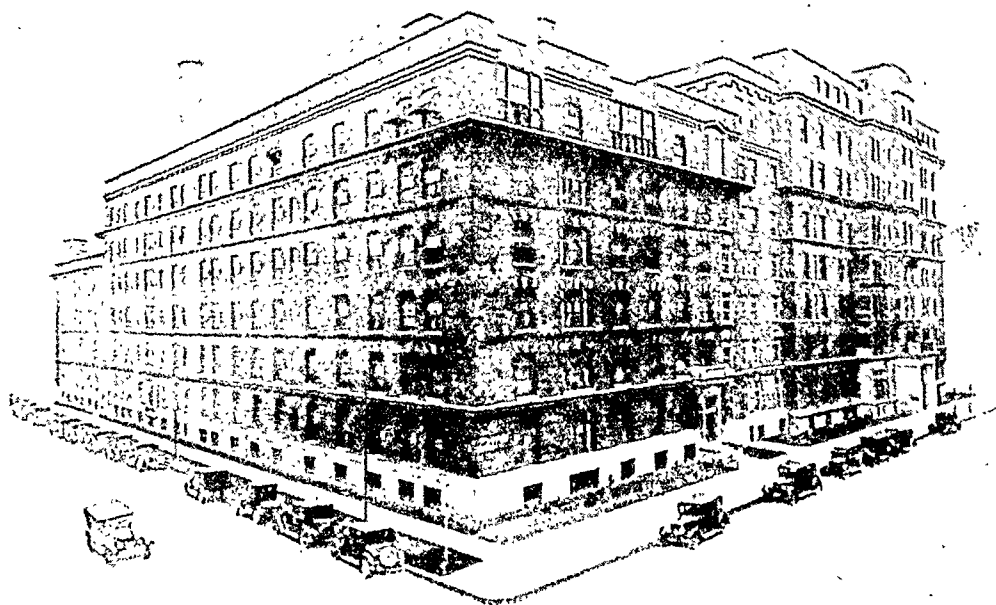


FIG. 8. Presbyterian Hospital.

country home for convalescent children at Prince Crossing, in part owned by the University and in part controlled by them, offer unusual opportunities for the care and study of orthopedics as related to children.

The Chicago Lying-In Hospital and Dispensary was founded in 1895 in four rooms located in a poverty stricken neighborhood. Today it has a modern hospital with a capacity of 260 beds. It is an outgrowth of years of intensive effort on the part of Dr. Joseph B. DeLee and a group of devoted supporters. The Dispensary on Maxwell Street gives treatment annually to more than 3,000 women during confinement in their homes. It is a teaching institution, being attended yearly by about 250 students of universities of the central states and nurses from 16 affiliated schools of nursing. The Chicago Lying-In Hospital and Dispensary is independently owned but became a unit of the University of Chicago Clinics in 1926.

Also affiliated with the University of Chicago, though not on its campus, is the Children's Memorial Hospital. This was founded in 1884 by Mrs. Julia F. Porter in memory of her son. It was reorganized in 1903 and its present name given to it. It is well known as a hospital in which excellent care is given to children not over the age of 13, and in which much investigative work of importance in medicine, surgery and the specialties has been carried on.

Under the guidance of the University of Chicago is Provident Hospital, founded in 1891 by a group of public spirited men of Chicago. Recently the hospital has moved into its new quarters and today is one of the most modern and outstanding negro hospitals in the world. It furnishes excellent opportunities not only for the care of negro patients, but for the training of colored interns and physicians.

Medical Societies. Chicago deserves consideration as a medical center because of the number of medical societies and famous medical organizations which have established their headquarters in that city.

At the head of these in importance and influence is the American Medical Association, the largest medical association in the world, with headquarters at 535 N. Dearborn Street. It was founded in Philadelphia in May 1847. The nature of the American Medical Association, its growth and its objects are so familiar to physicians as to need little comment. The names of two Chicago men come to mind in connection with the work of the Association, one that of N. S. Davis, the founder, and the other that of George H. Simmons, for many years its secretary, whose genius guided the Association in its marvelous development.

To many doctors the various councils and bureaus and special departments are but names. If visitors from the College of Physicians will but go to the American Medical Association headquarters and see the well organized, smoothly running activities of these various groups, they will be convinced of the magnitude of the undertaking and the efficiency with which the work is done. They will have renewed pride in our great American Medical Association.

Several noteworthy journals are published by the Association. In addition to the *Journal of the American Medical Association*, which was established in 1883 and is the leading medical journal in the United States and has the largest circulation of any medical journal in the world, the Association publishes the well known series of "Archives" of various specialties, and the *American Journal of Diseases of Children*. It also publishes the *Quarterly Cumulative Index Medicus*, the *American Medical Directory* and *Hygeia*.

The American Hospital Association, a charitable and educational association of hospitals and hospital people, is located in Chicago at 18 E. Division Street. Organized in Cleveland in 1899 with a membership of nine people, it has grown until now it numbers 1,533 institutions in the United States and Canada, and 2,646 leading administrators, members of

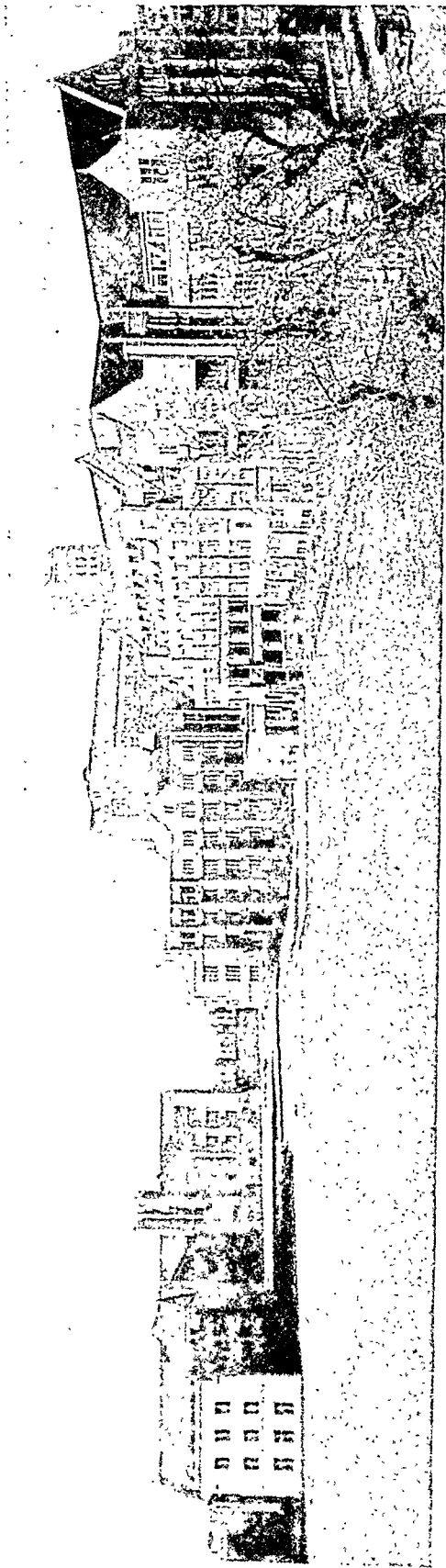


FIG. 9. Research and Educational Hospital group and University of Illinois College of Medicine.

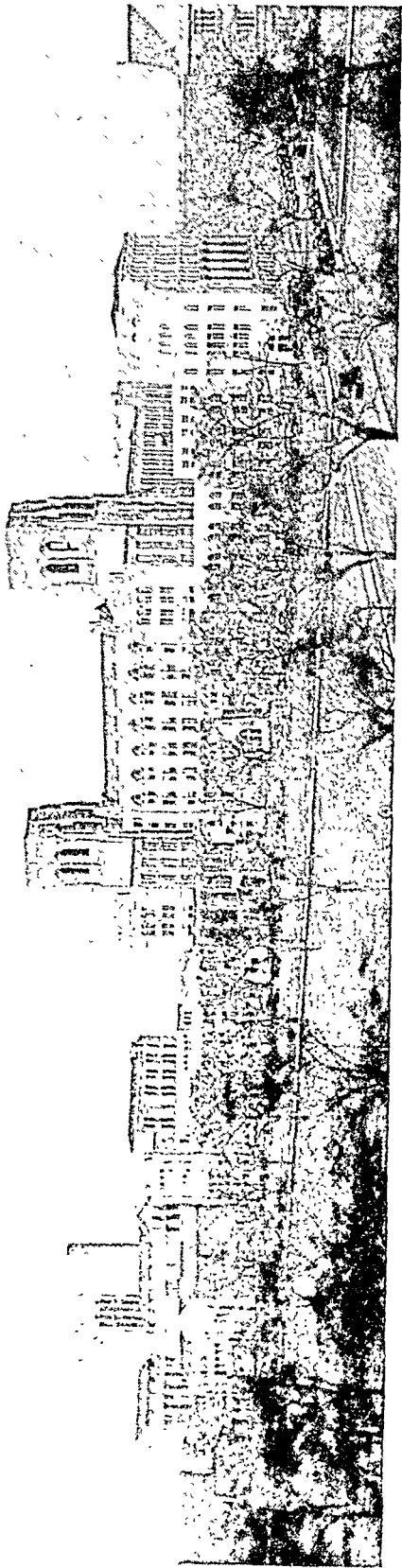


FIG. 10. University of Chicago Clinics.

boards of trustees and of medical and nursing staffs, and heads of departments. During the 35 years of its history the Association has spent more than a million dollars in the development of those principles and practices which have in a very large way assisted more than 7,000 institutions.

The American College of Surgeons with headquarters at 40 E. Erie Street has at the present time 11,214 Fellows, who are practicing surgery in North and South America. For 16 years the American College of Surgeons has conducted as one of its important activities the hospital standardization movement. It has spent in the neighborhood of one million dollars in making thousands of individual surveys of hospitals. As a

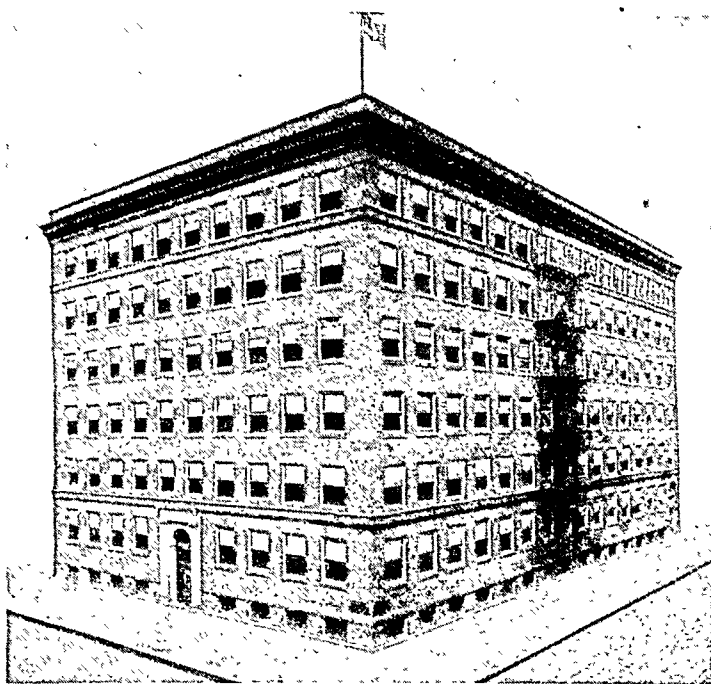


FIG. 11. American Medical Association.

result it has been a powerful influence in eliminating commercial and unscientific features from many hospitals in this country. The standards of these institutions have been distinctly raised, and the care of the sick and the training of the staff and of undergraduates have been definitely improved. The College sponsors a number of other important activities. We mention the library and department of literary research which provide physicians with abstracts, bibliographies, package libraries, etc. There is also a department of clinical research which is investigating such subjects as bone sarcoma, the treatment of malignant disease, and the treatment of fractures.

We should mention also *Surgery, Gynecology and Obstetrics*, the official publication of the American College of Surgeons. This monthly journal

was started in 1905, edited by "active surgeons for active surgeons," and today is recognized as one of the leading surgical publications of the world.

There are many medical societies. Nearly all the specialties are represented by local societies. The parent society of all, the Chicago Medical Society, has been in existence since 1850. At the present time there is a central body known as the Chicago Medical Society, with a membership which is considered to be the largest in the world. Scientific meetings are held each week. Then there are 15 branches of this central body, each branch selecting its own officers and holding scientific meetings once a month. The Chicago Medical Society coöperates with the State Society in various ways, as for instance through its Educational Committee, whose headquarters are in Chicago. The *Illinois Medical Journal*, a monthly magazine, the official journal of the organization, is published in Chicago.

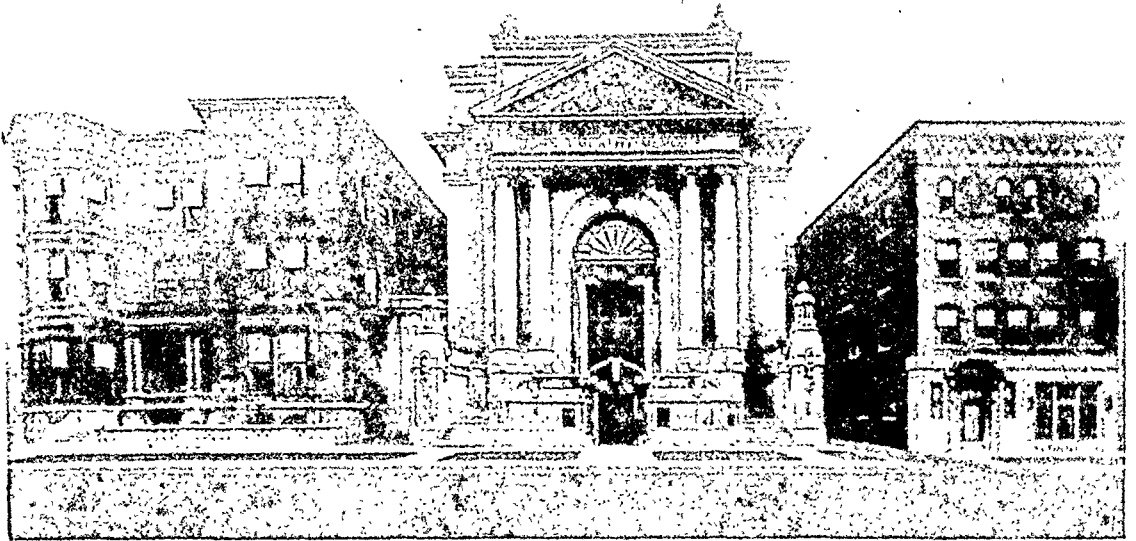


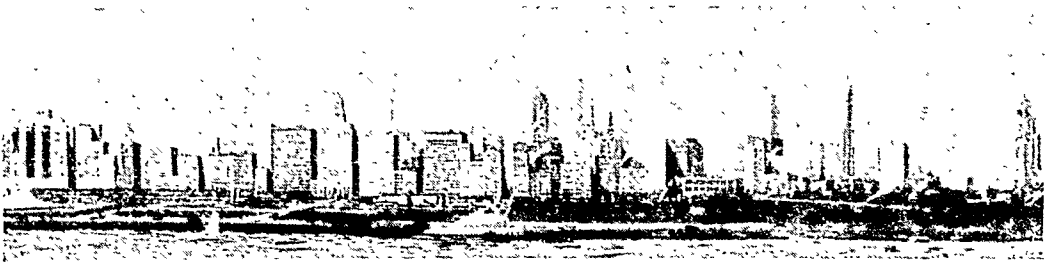
FIG. 12. American College of Surgeons group, showing main building (left); John B. Murphy Memorial (center); and Surgery, Gynecology, and Obstetrics building (right).

The Institute of Medicine of Chicago has been in existence for some 15 years. It is modeled after the College of Physicians of Philadelphia, the New York Academy of Medicine and similar organizations. Its membership of about 400 is carefully selected. It sponsors and encourages high grade practice of medicine, investigation in medicine and related sciences, and medical features that are of interest to the public. Though comparatively young, its activities have already been productive of great good.

The visiting members of the American College of Physicians and their wives will find many interesting features in Chicago aside from its medical landmarks. A more detailed description of these will be given in a folder which is to be issued at the time of the meeting. We may mention here, however, the Adler Planetarium and Astronomical Museum, the Art Insti-

tute, the Chicago Historical Society, the Chicago Museum of Natural History, The Field Museum, the Shedd Aquarium, the Museum of Science and Industry, The Oriental Institute, to say nothing of the Stock Yards, the great mail order houses, the Board of Trade and other business enterprises.

Many will wish to attend the concerts of the Symphony Orchestra or of other musical organizations which will be given during the meeting of the College; or to visit the numerous theaters. Public lectures are held weekly at the various universities. Excursions may be made around the miles of boulevard and park that surround the city, with stops at the various points of interest.



EDITORIALS

PROGRESS OR RETROGRESS

PHYSICIANS can be divided into two great groups, those that are learning and those that are forgetting, those that each year know more, and those that each year know less. There seems no third group, those that are stationary.

A few physicians increase in knowledge from within and grow from their own doing. These are the innate investigators. The rank and file require outside help to grow and to progress. Books, meetings, contacts, discussions, teachers, are our armamentarium for progress. Like the "spring tonic" of past days, all of us need some of this medicine, at least annually, better if it comes more frequently. A large majority of physicians know their need and seek treatment.

Things in nature rarely are static; they increase or they decrease; they grow or they decay; they progress or they retrogress. Man's education in many respects resembles things of nature; rarely is it static; when knowledge does not increase, almost always it decreases. Physicians should remember this and make every effort to keep out of the static state and on the side of increase, of growth, of progress.

Contact with colleagues eager to learn, listening to discussions by those capable of teaching, witnessing demonstrations and clinics, seeing scientific exhibits lead to more reading and better observation of patients. Herein lies medical progress. The meeting of the American College of Physicians provides just these opportunities. Attendance at this meeting is a potent way for a physician to get himself out of the group of those who each year know less. The stimulus received from attendance at a medical meeting where men eminent in the profession speak lasts long after the meeting is over.

HENRY A. CHRISTIAN, M.D., F.A.C.P.

THE NEW PURE FOOD AND DRUG BILL

AT THE special session of Congress last summer, Senator Copeland introduced the first draft of a bill which was designed to replace the present federal law governing the manufacture and sale of foods and drugs. The Food and Drugs Act of 1906, which was drafted by the late Dr. Harvey W. Wiley and was pushed through Congress in spite of tremendous opposition, was considered very comprehensive in scope, but time has indicated that it is not sufficiently broad in its terms to meet the needs of the present day.

The most serious omission in the Wiley act lies in its failure to give power to the Food and Drug Administration to curb the excessive and often fraudulent claims in the advertising matter issued by the less conscientious manufacturers of drugs and foods. False labeling of the con-

tainer is penalized but the far more effective propaganda of lying advertisements is beyond the reach of the law.

The use of dangerous adulterants or the addition of harmful preservatives is fairly well controlled at present, but adulteration with harmless ingredients and the sale of substandard products are difficult to control. The use of a "distinctive name" for the product permits it to escape conviction under the law.

The phraseology of the present law requires that to obtain conviction of false labeling the Food and Drug Administration must prove that the statements made are both *false* and *fraudulent*. In other words it must be shown that the manufacturer realized the falsity of his claims. The manufacturer has only to exhibit a few signed testimonials from users of his product to render plausible his statement of belief in its efficacy. It is not often that the federal authorities have as ready a rebuttal as in a recent case which was tried in Baltimore. The defendant had been selling a consumption cure consisting chiefly of turpentine and egg albumin. He based his defense largely on testimonials from patients. A federal officer was able to show, however, that of a series of testimonials from one individual, several were dated after the ascertained time of this person's death. It was eventually proved that the manufacturer had been paying for these letters and that after the death of the original author he had knowingly continued to pay the son for further testimonials to the "cure."

The present law is also defective in that it makes no provision for the supervision of the manufacture and sale of a number of chemical compounds and mechanical appliances which may seriously affect the health of those who use them. Cosmetics, for example, are not under federal supervision as to the nature of the ingredients, the conditions of manufacture or the truthfulness of the label. Medical men since 1906 have had opportunity to learn of the harm that may result from hair removers, dyes, facial creams and powders. The *Journal of the American Medical Association* has done much to keep the profession, and through them the public, informed of such dangers. Usually, however, it has been only the damage suits of the injured that have had power to force the manufacturer to discontinue the sale of his product.

Along with cosmetics, various obesity cures, radium waters, electrical belts, nose straighteners, etc., now escape legal control.

The bill introduced by Senator Copeland last summer goes a long way toward closing the loop holes which exist in the present law. According to its terms a statement of the ingredients of a compound would have to be printed not only on the label of the package, but as a part of any advertising matter. Certain incurable diseases are specified and no advertisement of a "cure" for these would be permitted. Medicines which in general medical opinion are only palliative in their effect would have to be so labeled. Cosmetics, reducing compounds and mechano-therapeutic devices would by the new act be brought under federal control. Definite standards are men-

tioned by which the purity and strength of drugs would be measured, and others to govern quality of foods. Very large powers would be granted to the Secretary of Agriculture both to promulgate regulations in the spirit of the law and to inspect and if necessary regulate the methods of manufacture. The existing penalties for misbranding, etc., would be materially increased and equally stiff penalties would follow conviction for false advertising.

The medical profession was not surprised when the introduction of the Copeland bill aroused hot opposition on the part of the manufacturers of patent medicines and of various nostrums. It was hoped that these complaints indicated that the terms of the new act would effectively hamstring some of these concerns. But when widely known and reputable drug manufacturers were found in opposition there seemed to be some cause for astonishment.

The honest objections to the bill may be briefly summarized. It is pointed out by some of its opponents that the adoption of a new act will nullify the value of the great body of favorable court decisions which have been rendered in prosecutions under the present law and that it will take years of legal battles before the new law could be as effective. Moreover, since many of the state laws are modeled after the present federal law there would be endless confusion until all state laws were revised. Such revision might in some instances be delayed through the political strength of the interests affected. The program advocated by those who are impressed by these arguments is to retain the present law but to amend it so that its more serious omissions will be adequately covered. A measure containing such amendments has already been introduced before the House of Representatives.

Many of those who concede that changed conditions have made a new bill necessary are honestly critical of certain phrases in the first draft of the Copeland bill. They feel, for example, that to declare that advertising matter may be false by "inference or ambiguity" is likely to expose even honest advertising to attack. They are not willing that decisions should be made in accord with "the general agreement of medical opinion." Probably many jurists would adhere to their point of view that such "general agreement" has proved in the past to be quite rare.

The creation of an army of inspectors to work in the manufacturer's plant is feared by many; and there is question of the right of the government to make public secret formulae and technical processes. Finally there is strong and legitimate opposition to the almost unlimited regulating powers which would be granted to the Secretary of Agriculture.

The strength of the opposition has led to the introduction in the present Congress of a revised form of the Copeland bill in which changes have been made to meet the more valid arguments against the first draft. The objectionable phases cited above have been eliminated. Secret technical processes are protected. The discretionary powers of the Secretary of State are very

much restricted. Two committees of five are to be appointed by the President, one having authority in the issuance of regulations concerning drugs and the other having similar powers as to regulations concerning foods. The Secretary of Agriculture will initiate regulations by pointing out their necessity to the committee concerned, but the form of the regulation will be determined by the majority vote of the committee whose decision will have the force of law.

The revised Copeland bill is said to be an administration measure and as such is likely to become law. It is important that sufficient time be given to its consideration by all concerned so that in its final form it may prove to be workable and effective and, at the same time, just to the public, the drug, food and cosmetic industries, and the medical profession.

The conscientious manufacturer is entitled to protection against the false advertising and substandard products of unscrupulous competitors. The physician and the pharmacist should be aided by the assurance of better standardized products. But most of all the general public should receive more protection against the advertising campaigns of patent medicine and nostrum makers who prey on the human desire for quick remedies and for cures of the incurable.

It is estimated that the sum of 360 million dollars is spent annually in this country on self medication with patent medicines other than simple home remedies. This folly, of course, will not be overcome by the passing of a new bill. Its roots lie too deep in human ignorance and superstition. Something will be accomplished, however, by stopping the encouragement of this human weakness through deceptive advertising, and by rendering the quack remedies which the public demands at least harmless in content.

The voice of the medical profession should be heard in strong support of the revised Copeland bill. The American Medical Association has for years through its Councils on Pharmacy and Chemistry, Committee on Foods and Council on Physical Therapy, advised the profession in these fields. It stands in the position of natural leadership and should place the influence of the medical profession behind the passage of a strong bill and its adequate enforcement.

REVIEWS

Malaria Treatment of Parenchymatous Syphilis of the Central Nervous System. Supplement No. 107 to Public Health Reports. By R. A. VONDERLEHR, Passed Assistant Surgeon, United States Public Health Service. Government Printing Office, Washington. 1933.

The favorable results obtained by the induction of malaria fever in the treatment of syphilis, and particularly syphilis of the central nervous system, make this paper of interest. The clinical results obtained in the treatment of parenchymatous neurosyphilis in 8,038 cases are noted by years. A summarization of these results shows that 26 per cent of the cases were able to resume their former occupation, 22.3 per cent were improved, 28.3 per cent were unimproved and 23.4 per cent had died since the induction of the malaria. The communicability of induced malaria to the general population is an important public health problem and is considered in some detail. The histologic changes in the central nervous system and various theories as to the mode of action of the plasmodial disease upon syphilis of the central nervous system are considered. The technic of malaria inoculation as well as the treatment of the induced malaria are taken up. Brief consideration is also given to the question of prognosis. Contraindications to the induction of malaria which have been noted by a number of writers are described; those most commonly mentioned are cachexia, severe organic heart disease, tuberculosis, and nephritis, and other less common contraindications are listed. Serological changes taking place in the spinal fluid are described in some detail and various administrative and sociologic problems are discussed. The complications and sequelae of malaria therapy are also described.

In addition to the treatment of parenchymatous syphilis, consideration is also given to the subject of prophylactic action of malaria in the prevention of the development of syphilis of the central nervous system and to the treatment of other forms of syphilis. A complete bibliography through the year 1931 is appended.

W. L. T.

Radiologic Maxims. By HAROLD SWANBERG, B.Sc., M.D., F.A.C.P. 127 pages; 14 × 20 cm. Radiological Review Publishing Company, Quincy, Illinois. 1932. Price, \$1.50.

The maxims in this small volume cover the broad field in which roentgenology and radium therapy are of value. They will be of interest to the internist and the surgeon. Both will note, however, a certain optimism as to the value diagnostically and therapeutically of the radiologic method. A maxim or so on the value of co-operation between the clinician and the radiologist might well have been added.

M. C. P.

New Introductory Lectures on Psychoanalysis. By SIGMUND FREUD, M.D., LL.D.; translated by W. J. H. SPROTT. 257 pages. W. W. Norton and Co., New York. 1933. Price, \$3.00.

The Interpretation of Dreams. By SIGMUND FREUD, M.D., LL.D.; translated by A. A. BRILL, M.D., Columbia University. 600 pages. MacMillan Co., New York. 1933. Price, \$5.00.

It is very logical that these two books should be reviewed together as they form an excellent symposium on the science and art of psychoanalysis. Both books are up-to-date revisions of Freud's work which made its first appearance in 1900 and which aroused the scientific world to a more constructive understanding of the workings of the human mind. Dr. Brill rightfully says in his introduction: "No work on psychology worthy of its name can now afford to ignore Freud's theories. . . .

They have exerted the greatest influences on the mental sciences and have practically rewritten them."

The interpretation of dreams has been a popular subject for discussion for many hundreds of years, and Freud carefully surveys the scientific literature on dreams up to 1900. He then, in a logical sequence, first discusses the method of dream interpretation—the dream as wish fulfillment, distortion in dreams, the material and sources of dreams, how the dream works, the psychology of the dream-processes, and finally ends up by giving a complete bibliography of 461 items. As Freud says: "With an appreciation of the mode of functioning of the psychic apparatus and an insight into the relation between conscious and unconscious, all that is ethically offensive in our dream-life and the life of fantasy for the most part disappears."

Freud gave his First Introductory Lectures on Psychoanalysis in 1915, and this more recent volume of lectures was prepared in the summer of 1932 in Vienna. As he states in his preface, these lectures "are addressed to that large group of educated persons to whom, let up hope, one can ascribe a benevolent, if cautious, interest in the special nature and discoveries of this young science. . . . It looks as though people did not expect from psychology progress in knowledge, but some other kind of satisfaction; every unsolved problem, every acknowledged uncertainty is turned into a ground of complaint against it." In seven chapters Freud then discusses the basic factors in the psychoanalytic process. He first takes up the interpretation of dreams, but this discussion in no way can replace the more exhaustive treatment of this subject given in his larger volume. He then discusses "the anatomy of the mental personality, anxiety and instinctual life, the psychology of woman, a philosophy of life and psychoanalytic explanations, complications and orientations."

Any person interested in a thorough study of psychoanalytic method cannot do better than to begin with the reading of these two books and continue by reading *Psychoanalysis and Medicine* by Karin Stephen, a book which was reviewed in the December issue of *THE ANNALS*. But the reader must remember, as Freud says in his introductory lectures: "It is exceedingly difficult to give an insight into the psychoanalysis to any one who is not himself a psychoanalyst. I assure you that we do not like to give the effect of being members of a secret society carrying on a secret science. And yet we have been obliged to recognize and state as our considered opinion that no one has a right to a say in psychoanalysis unless he has been through certain experiences which he can only have by being analyzed himself." But as Freud concludes in his *Interpretation of Dreams*: "For all practical purposes in judging human character, a man's actions and conscious expressions of thought are in most cases sufficient. Actions, above all, deserve to be placed in the front rank; for many impulses which penetrate into consciousness are neutralized by real forces in the psychic life before they find issue in action; indeed, the reason why they frequently do not encounter any psychic obstacle on their path is because the unconscious is certain of their meeting that resistance later. In any case, it is highly instructive to learn something of the intensively tilled soil from which our virtues proudly emerge. For the complexity of human character, dynamically moved in all directions, very rarely commits itself to the arbitrament of a simple alternative, as our antiquated moral philosophy would have it."

J. L. McC.

Hygiene of the Mind. By BARON ERNST VON FEUCHTERSLEBEN; translated from the German by F. C. SUMNER, Ph.D., Professor of Psychology, Howard University, Washington, D. C. 150 pages. MacMillan Company, New York. Price, \$1.25.

This little book is uniquely interesting as it was written about 100 years ago by an Austrian physician, philosopher and poet, who obtained his medical degree in 1833. As Dr. Esther Loring Richards says in the introduction, the author must have been an astute observer and a reflective physician who in the course of his practice of

medicine learned to see his patients functioning as total personalities and not as physiological segments.

The author states, "I like the reader who wishes to be stimulated rather than dogmatized. The doubtful appears more interesting to me than that which has been settled. Let each one proceed with his own feet through the fields whither I point. It seems to me altogether true that all virtue is self-mastery, although not all self-mastery is virtue."

It is well for persons in this day and age, who frequently belie the fact that we are rapidly going to the dogs, to stop for a moment and read the first few lines of the introductory chapter of this very old book which states that: "Our age is fast, impetuous and frivolous. One does himself and the reading public a real mental service if one directs the gaze away from the discouraging life of a volcanic present, or from the still more discouraging vacillating literature which is falling to pieces in a thousand futile directions toward the quiet regions of the science of the inner man toward the contemplation of our Self."

He further on states: "Perhaps physicians and we ourselves have not yet devoted to this viewpoint the full attention which it deserves. For here it is a question of being one's own physician before being a physician to others." And he makes a very modern axiom of mental hygiene when he advises us "to analyze man instead of gaping at him as at a miracle."

There is no doubt that the reader could spend several stimulating hours between the covers of this book. And, although it is not written exactly in the language of our day, we come to the conclusion that the sages of the past have yet a great deal to teach us.

J. L. McC.

Diseases of Old Age. By F. MARTAN LIPSCOMB, M.R.C.P. (London), Major Royal Army Medical Corps, Deputy Surgeon of the Royal Hospital, Chelsea. vii + 472 pages; 13 × 19 cm. William Wood and Company, Baltimore. 1933. Price, \$4.50.

The author has produced a very readable account of the clinical characteristics of diseases in the aged, i.e. in those above the age of 65 years. He reminds the reader quite rightly that with the decrease in infant and early adult mortality, the care of the aged is becoming an increasingly larger part of the physician's task. Many diseases are not greatly altered by the age of the patients but others show very different clinical features and still others are practically confined to the later periods of life. The book deals only with these last two categories. The clinical descriptions for the most part have the freshness derived from personal observations. The therapeutic recommendations are sane and specific. The large field covered makes brevity a requisite and at times one feels that this has resulted in inadequacy. The chapter on the nervous system is an example of excessive condensation. One might mention here that the omission of pernicious anemia as a cause of senile paraplegia is unfortunate since early detection and treatment may arrest the progress of the condition. On the other hand, this undue brevity is in part compensated for by the carefully selected references which add much to the value of the book. It is a little volume which should prove of very real value to all practitioners.

M. C. P.

COLLEGE NEWS NOTES

NOMINATIONS FOR ELECTIVE OFFICES

1934-35

The Nominating Committee herewith transmits the following nominations for elective offices of the American College of Physicians for the year 1934-1935:

President-ElectJames Alex. Miller, New York, N. Y.

First Vice-PresidentJames H. Means, Boston, Mass.

Second Vice-PresidentRandolph Lyons, New Orleans, La.

Third Vice-PresidentJames F. Churchill, San Diego, Calif.

Respectfully submitted,

per directions of the Committee,

JOHN H. MUSSER, *Chairman*.

Attest: E. R. LOVELAND.

December 27, 1933

Acknowledgment is made of the following gifts of publications to the Library by members of the College:

Dr. Franklin B. Bogart (Fellow), Chattanooga, Tenn.—five reprints;

Dr. A. Morris Ginsberg (Fellow), Kansas city, Mo.—three reprints;

Dr. Murray B. Gordon (Fellow), Brooklyn, N. Y.—six reprints;

Dr. Edward G. Huber (Fellow), Lt. Col., M. C., U. S. Army—two reprints;

Dr. Hyman I. Goldstein (Associate), Camden, N. J.—one reprint;

Dr. Arthur H. Jackson (Associate), Washington, Conn.—one reprint;

Dr. Frederick W. Mulsow (Associate), Cedar Rapids, Ia.—two reprints.

Major John G. Knauer (Associate), Medical Corps, U. S. Army, has been transferred from Balboa Heights, Canal Zone, to Ancon, Canal Zone, where he is assistant to the Chief of the Medical Service, and Cardiologist to the Gorgas Hospital.

Dr. Howard T. Karsner, professor and director of the Institute of Pathology of the School of Medicine of Western Reserve University, Cleveland, delivered the Smith-Reed-Russell Lecture at the School of Medicine of George Washington University, Washington, D. C., on December 19. He spoke on "Rheumatic Heart Disease."

Dr. Murray B. Gordon (Fellow), Brooklyn, New York, addressed the Buffalo Academy of Medicine on "Criteria of Endocrine Disorders in Children" on November 22, 1933.

Dr. Benjamin Goldberg (Fellow), associate professor of medicine, University of Illinois College of Medicine, has been given an honorary professorship in the National University of Mexico.

Dr. James Alexander Miller (Fellow), New York City, presided at the laying of a seven ton cornerstone for the new building of the Departments of Health, Sanitation and Hospitals in New York City recently. The work was originally begun in 1931. The building will occupy an entire block, and will be ten stories high.

Dr. Henry J. John (Fellow), Cleveland, Ohio, has been appointed head of the newly created department of metabolic diseases at St. Luke's Hospital, Cleveland.

Under the auspices of the Division of University Extension of the Massachusetts State Department of Education and the Massachusetts Society for Mental Hygiene,

a course of lectures were recently given on intelligent living and on the adjustments of normal youth. Dr. Joseph H. Pratt (Fellow), Boston, gave a lecture on "The Body and the Mind" and Dr. Austen Fox Riggs (Fellow), Stockbridge, gave a lecture on "Intelligent Living."

Recently Dr. Albert H. Hoge (Fellow), Bluefield, was reappointed and Dr. Walter E. Vest (Fellow), Huntington, was newly appointed to the Public Health Council of West Virginia.

Dr. Eugene E. Murphey (Fellow), Augusta, Ga., has been elected to the Board of Trustees of the University of Georgia Hospital.

Captain Edward U. Reed, M. C., U. S. Navy (Fellow), has been ordered from command of the U. S. Navy Dispensary, San Pedro, Calif., to command the U. S. Naval Hospital, Charleston, S. C.

Dr. Franklin B. Bogart (Fellow), Chattanooga, Tenn., has been elected secretary of the Section on Radiology of the Southern Medical Association. Dr. Bogart has also been elected president of the Chattanooga and Hamilton County Medical Society for 1934.

At the last annual meeting of the American Student Health Association held in Chicago, December 27-29, 1933, Dr. R. W. Bradshaw (Associate), College Physician of Oberlin College, Oberlin, Ohio, was elected president.

Dr. Harold F. Machlan (Fellow) has been officially transferred to Washington, D. C., as Medical Supervisor, Central Office of the Veterans Administration. Dr. Machlan was formerly Clinical Director of the U. S. Veterans Administration Hospital at Dayton, Ohio.

Major Edgar Erskine Hume (Fellow), librarian of the Army Medical Library, Washington, D. C., has been awarded the Wellcome Prize for 1933, consisting of \$500.00 and a gold medal, by the Association of Military Surgeons of the United States at its last annual meeting in Chicago. The prize was awarded for Major Hume's essay on "The Value of Studies in Health and Sanitation in War Planning."

After fifteen years' service as editor of the *Virginia Medical Monthly*, Dr. Alexander G. Brown, Jr. (Fellow), Richmond, Va., has resigned. For the same period of time, Dr. Brown was chairman of the Program Committee of the Medical Society of Virginia.

Dr. Francis H. Smith (Fellow), Abingdon, Va., is now president-elect of the Medical Society of Virginia.

At the last annual meeting of the Southern Medical Association, in Richmond, during November 1933, the following Fellows of the American College of Physicians were elected to the offices indicated: Dr. H. Leslie Moore, Dallas, Texas, president; Dr. Thomas A. Groover, Washington, D. C., second vice-president; Dr. Seale Harris, Birmingham, Ala., chairman of the Board of Trustees; Dr. William B. Porter, Richmond, secretary of the Section on Medicine. Dr. William deB. MacNider, professor of pharmacology at the University of North Carolina, received the annual medal for outstanding achievements in original research. Dr. Glenville Giddings received first award for scientific exhibits, and Dr. George B. Lawson, Roanoke, received honorable mention.

OBITUARIES

DR. GEORGE J. ECKEL

Dr. George J. Eckel (Fellow), Buffalo, N. Y., was born February 16, 1878, at Perrysburg, Ohio, and died October 29, 1933, in Buffalo, N. Y. He was graduated from the Perrysburg (Ohio) High School in 1898 and graduated from Canisius College with the degree of A.B. in 1903 and the degree of A.M. in 1904, and from the University of Buffalo with the degree of M.D. in 1908. He did postgraduate study in London, England, in 1916, with Dr. Thomas Lewis and in Vienna, Austria, in 1923, with Dr. Erdheim and others.

He was appointed Assistant Professor of Medicine in the University of Buffalo in 1921, Associate Professor of Medicine in 1927, and Clinical Assistant in Medicine, Buffalo General Hospital, in 1920, Consulting Internist to the U. S. Public Health Service in 1924. He was a member of the Faculty of the Medical Department of the University of Buffalo in 1910 and Attending Specialist in Internal Medicine, U. S. Marine Hospital, in 1933.

At the time of his death, he was a member of the Staff of the Buffalo General Hospital, Buffalo, Emergency Hospital, Buffalo City Hospital, Eye and Ear Dispensary and Wettlaufer Clinic, Mount Mercy Hospital and Crippled Children's Guild. He was consultant to the Staffs of the U. S. Marine Hospital and Our Lady of Victory Hospital.

Dr. George Eckel entered the U. S. Navy, April 21, 1917, as Lieutenant, Junior Grade, Medical Corps, and was discharged from the Service September 16, 1919, as Lieutenant, Senior Grade. He served at the Marine Headquarters, Buffalo, N. Y., April 21, 1917 to October 20, 1918; at receiving ship in New York City, October 24, 1918, to November 23, 1918; on board the U. S. S. *George Washington*, November 23, 1918, to April 10, 1919; at Marine Headquarters, Buffalo, from April 13, 1919, to September 16, 1919. He attended the Military Instruction Camp under the War Department, U. S. Army, in 1916.

The squad from the Naval Militia (New York) fired the salute over his grave and taps were sounded as a final tribute for his medical service during the World War.

He was a member of The American College of Physicians (1921), American Medical Association, Buffalo Academy of Medicine, Erie County Medical Society, New York State Medical Society, Society for the Study and Prevention of Cancer, Alumni Association of the Medical Department of the University of Buffalo, and of Omega Upsilon Phi, national fraternity.

He was a member of the War Society of Cruiser and Transport Service, Veterans of Foreign Wars, U. S. Naval Reserve, Post 368, Crew of the U. S. S. *George Washington*, American Red Cross, Buffalo Society of Natural Science, Erie County Society for Prevention of Cruelty to Animals.

U. S. Training Camp Association, Automobile Club of Buffalo and American Historical Society.

Dr. George Eckel had a sunny and cheery disposition, his clinical presence was pleasant and reassuring; his knowledge of medicine was deep and wide. He was an excellent diagnostician and a safe adviser. He was up-to-date in his methods. As a teacher he was well liked by his students and by other members of the teaching staff. His hospital work was good. His kindness to the ward patients was outstanding and unfailing. He had an extensive consultation practice. He was widely known among the members of the American College of Physicians and the many other medical organizations of which he was a member. His associates in medicine were always glad to see him and to return his hearty and cordial greeting. He died altogether too young, and we mourn his loss and miss him much.

ALLEN A. JONES, M.D., F.A.C.P.,
Governor for Western New York.

DR. ADRIAN HANSFORD GRIGG

Adrian Hansford Grigg, M.D. (Fellow), Beckley, W. Va., died of pneumonia after a week's illness on January 6, 1934, at the Beckley General Hospital where he had been chief of the Medical staff for over twelve years.

Dr. Grigg was born at Crown Hill, West Virginia, August 1888, and was educated in the public schools and the West Virginia University. He graduated with honors at Jefferson Medical College in 1912, being elected a member of Alpha Omega Alpha. He served his internship at the Philadelphia General Hospital. In 1913 he located in West Virginia and entered the Medical Corps of the Navy, serving at the Naval Academy during the World War with the rank of Lieutenant.

On his return he became head of the Medical Service at the Beckley General Hospital and was instrumental in its development into one of the leading hospitals in the State.

He was a member of his county and state medical societies and of the American Medical Association. In 1929 he became a Fellow of the American College of Physicians. He was also a member of Beta Theta Pi.

He left a widow and one daughter.

R. D. ROLLER, JR., M.D., F.A.C.P.,
Charleston, W. Va.

NATIONAL PNEUMONIA SERA



The Research Laboratories of The National Drug Company have made close studies of producing and refining Pneumonia Serum. Methods of immunizing horses, and processes of concentrating and refining the serum, have been devised enabling us to offer a refined and concentrated product approximating six to ten times the potency of the unrefined serum, with a corresponding decrease of inert solids and proteins. Refined Pneumonia Serum contains at least 8500 Felton Units per 10 cc. and in addition all other specific antibodies and antitoxic or protective substances contained in the whole serum.

The chill producing substances have largely been removed.

Doses of 10 to 20 cc., repeated every six to eight hours, or as advisable, may be given until a favorable response is secured. The patient's sputum should be typed early and if Type I, II or III pneumococci are present the serum should be continued. When the type of pneumococcus in the sputum and blood is represented by antibodies or protective substances in the serum, reports from physicians show a fall in the patient's temperature as soon as sufficient serum has been given to overcome the bacteriemia and toxemia. Early and adequate doses of serum are essential to overcome the infection.

Refined Pneumonia Serum is furnished in 10 cc. perfected syringes, with chromium (rustless steel) intravenous needles, and in 20 cc. syringes and ampoule-vials.

For Quick Pneumonia Type Diagnosis

We prepare monovalent pneumonia typing serums for rapid typing of pneumonia by the Neufeld (quellung) reaction described by A. B. Sabin (Jour. Am. Med. Asso. 5-20-33 fol. 1584).

PTD-I	Five Tests (5 capillary tubes)	Type I	\$0.50
PTD-II	Five " (5 " ")	Type II	.50
PTD-III	Five " (5 " ")	Type III	.50
PTD I-5	Fifty or more Tests (5 cc. ampoule-vial)	Type I	\$2.00
PTD II-5	Fifty " " (5 " " ")	Type II	2.00
PTD III-5	Fifty " " (5 " " ")	Type III	2.00

Detailed information on request.

THE NATIONAL DRUG COMPANY
PHILADELPHIA
U.S.A.



Send detailed information on Refined Pneumonia Serum per Annals of Internal Medicine.

Name State

City Date

Hospital Consultation and Advisory Service

Often a definite fact-finding survey of an institution locates the source of annoying business and professional practices which seriously interfere with efficient care of patients and economical administration. This office conducts community or individual hospital surveys in an expert and confidential manner.

Office of

WILLIAM HENRY WALSH, M.D.

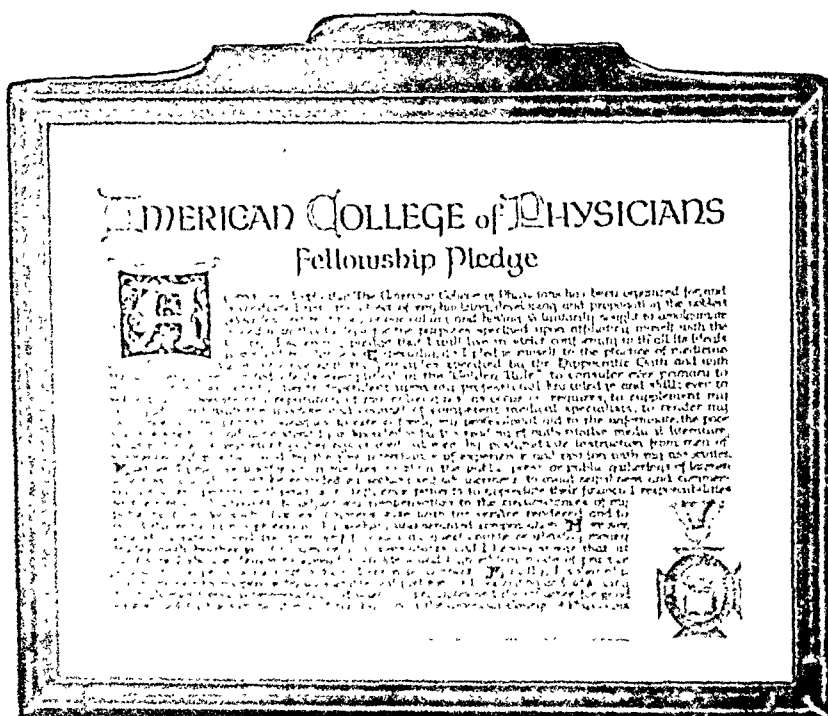
612 North Michigan Avenue

CHICAGO

The WYATT CLINIC for Chronic Arthritis

3

TUCSON, ARIZONA



FELLOWSHIP PLEDGE of the COLLEGE

Official Pledge
and Frame

Price \$6.00
Postpaid

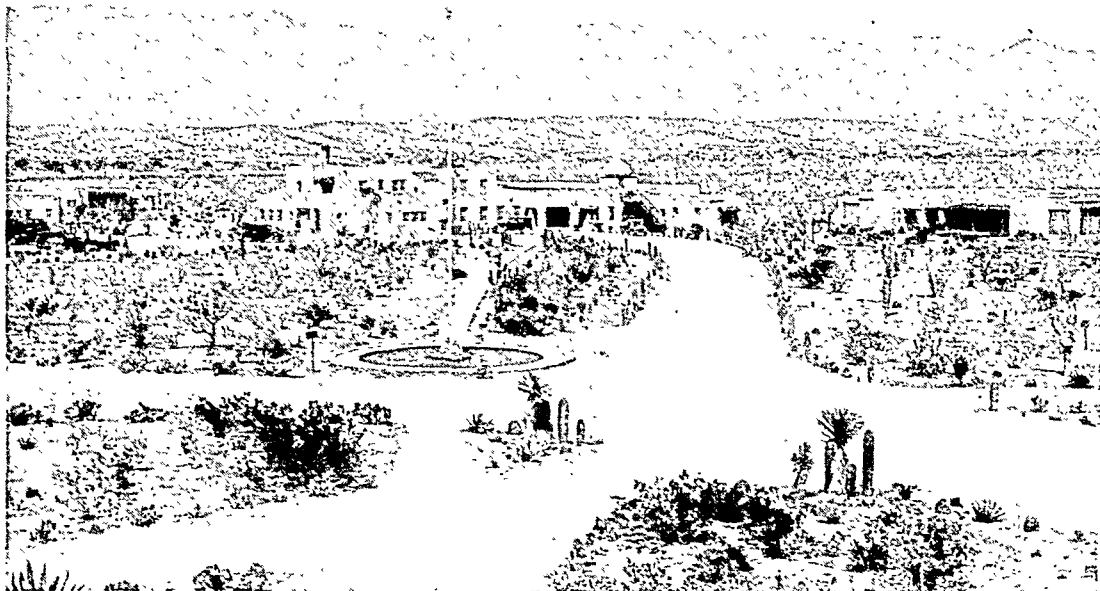
Every FELLOW of The American College of Physicians should display this Pledge in his office. It is engraved on parchment, and bears the seal and colors of The College.

Send orders to E. R. LOVELAND, Executive Secretary,
The American College of Physicians, 133-135 South 36th Street,
Philadelphia, Pa.

Please Mention this Journal when writing to Advertisers

The Desert Sanatorium and Institute of Research

Tucson, Arizona



Altitude 2,600 feet

Entering upon its eighth season, this well-known Institution affords the facilities of modern diagnosis and treatment under unexcelled climatic conditions. Its appointments represent the acme of attractiveness, comfort and convenience. Not a hospital for the treatment of pulmonary tuberculosis, it aims at the utmost perfection of diagnosis and treatment of every condition that may be benefited by a warm, dry, sunny climate of desert type, such as chronic arthritis, sinusitis, nontuberculous pulmonary and upper respiratory complaints, arterial hypertension, cardiorenal insufficiency, etc.

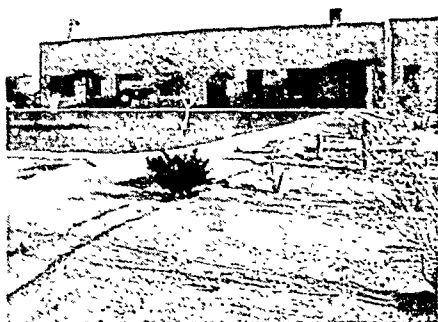
ALLEN K. KRAUSE, M.D., *Director*

W. PAUL HOLBROOK, M.D., *Physician-in-Chief*

VIVIAN TAPPAN, M.D., *In Charge of Pediatrics*

MAX PINNER, M.D., *Director of Laboratories*

CHARLES W. MILLS, M.D., *In Charge of Visiting Staff*



Recreation Centre



Out-Patient Clinic

WRITE FOR BOOKLET

For RATES AND OTHER INFORMATION

Address *Secretary, Desert Sanatorium*
Tucson, Arizona

"For the practitioner such a work is nearly indispensable" — *ANNALS OF INTERNAL MEDICINE*

**The
PRACTITIONERS
LIBRARY**

of Medicine and Surgery

GEORGE BLUMER, M.D., EDITOR

This important set offers in a single work of twelve volumes and supplement-index all the essentials of medicine and surgery. Dr. Blumer, its supervising editor, is Clinical Professor of Medicine, Yale University, School of Medicine, and for every volume there are one or more distinguished associate editors. The thousands of subjects covered are each treated by men who are of the highest standing and who are active and acknowledged authorities in their respective fields. Consistently written from the practitioner's viewpoint, thoroughly modern in the materials presented, and lavishly illustrated throughout, here is perhaps the greatest 20th Century contribution to the literature on general medical practice. *12 Vols. and Supplement-Index. 6 volumes now ready. Handsomely bound in buckram. \$10 per vol. (sold only as a set).*

"The undoubted standard...this edition will maintain its established reputation"

— *AMERICAN JOURNAL OF SURGERY*

New (10th) Edition---Holt and Howland's

**DISEASES OF INFANCY
AND CHILDHOOD**

Revised by *L. Emmett Holt, Jr., M.D.*, Associate Professor of Pediatrics, Johns Hopkins University; and *Rustin McIntosh, M.D.*, Carpentier Professor of Diseases of Children, Columbia University. No general practitioner should be without the new (10th) edition of "Holt." The revisions include: the addition of an unusually comprehensive bibliography; the allotment of more space to interpretation and pathogenesis; and the complete rewriting of the sections on Nutrition and Nutritional Disorders, Deficiency Diseases, Diseases of the Blood, and Diseases of Allergy; and many other extensive changes. Altogether the volume has been ably and significantly brought up to date, and it now continues to hold its place as the classic in its field. Profusely illustrated. \$10.00.



D. APPLETON - CENTURY COMPANY

35 West 32nd Street

New York City

LONG AWAITED ~ READY SOON

THE MEDICAL and ORTHOPAEDIC MANAGEMENT OF CHRONIC ARTHRITIS

By

Ralph Pemberton

and

Robert B. Osgood

M.S., M.D., F.A.C.P.

A.B., M.D., F.A.C.S.

Professor of Medicine, Graduate School of Medicine, University of Pennsylvania. Chairman American Committee for the Control of Rheumatism. Member Council on Physical Therapy of the American Medical Association, etc.

John Ball and Buckminster Brown Professor Emeritus of Orthopaedic Surgery, Harvard Medical School. Member American Committee for the Control of Rheumatism. Member Council on Physical Therapy of the American Medical Association, etc.

Publication early Spring

About 400 pages, Illustrated

Probable Price \$5.00

TABLE OF CONTENTS

1. History and Incidence of Arthritis
2. Classification of Chronic Arthritis
3. Gross and Microscopic Pathology of Chronic Arthritis
4. Physiological Disturbances Associated with Chronic Arthritis
5. Etiology 6. Symptomatology
7. Treatment—General Medical Principles, History, Examination, etc.
8. Treatment—Adjustments of the Major Bodily Systems; Mechanical Aids to Physiological Function
9. Treatment—Gastro-Intestinal Tract and Dietetics
10. Treatment—Physical Therapy
11. Treatment—Vaccines 12. Treatment—Drugs
13. Orthopaedic Appliances, Surgery of Chronic Arthritis
14. General Discussion

THE MACMILLAN COMPANY

Publishers

60 Fifth Avenue

New York

Please enter my }
order for }
Name..... } PEMBERTON and
Address..... } OSGOOD'S ARTHRITIS

*... There is a reason why
Pil. Digitalis (Davies,
Rose) have become the
choice of Cardiologists*



... They are digitalis in its completeness—physiologically tested leaves in the form of physiologically standardized pills, giving double assurance of dependability.

... Each pill contains 0.1 gram, the equivalent of about $1\frac{1}{2}$ grains of the leaf, or 15 minims of the tincture.

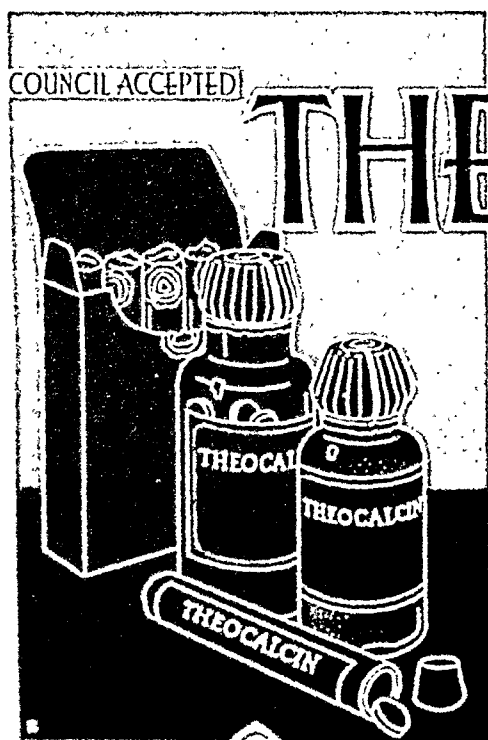
... Convenient, uniform, and more accurate than tincture drops.

Sample and literature upon request.

DAVIES, ROSE & CO., Ltd.

Pharmaceutical Manufacturers,

BOSTON, MASS.



THEOCALCIN

(theobromine-calcium salicylate)

A well tolerated diuretic and myocardial stimulant indicated in cardiovascular disease with, or without, renal insufficiency. . . .

$7\frac{1}{2}$ grain Tablets and Powder.

DOSE: $7\frac{1}{2}$ to $22\frac{1}{2}$ grains t. i. d.
with or directly after meals.

Literature and samples upon request.

BILHUBER-KNOLL CORP.

154 OGDEN AVENUE, - JERSEY CITY, N. J.

Please Mention this Journal when writing to Advertisers

Devitt's Camp, Inc.

ALLENWOOD
PENNSYLVANIA

(Tuberculosis)

*On beautiful White Deer Mountain, 20 miles southeast
of Williamsport, Pa.*

DEVITT'S CAMP was started in April of 1912 to take care of three men who would not leave their families. There was no intention of making it a tuberculosis sanatorium. The first patients slept in a barn. Since that time the Camp has grown until it comprises bed capacity for 115 patients, and has a staff of two full time physicians and eleven nurses. It is fully equipped to take care of persons suffering from pulmonary tuberculosis. It has grown in value from a barn to a value of \$348,000. We have endeavored to render the best service irrespective of cost. Special effort has always been made to make the surroundings cozy and homelike. We have always felt that the best asset of the Camp has been the spirit of cooperation which is maintained between the staff and the patients. Forty per cent of the patients are receiving artificial pneumothorax, and other operative procedures such as phrenicectomy, Jacobaeus operation, and thoracoplasty are taken care of in nearby surgical centers by skilled chest surgeons.

Devitt's Camp would be very glad to take care of your patients for you. A full report is sent to each family physician of every examination and x-ray. The rates are moderate—\$23.00 and \$30.00 per week which includes everything except personal laundry and necessary x-ray plates which are charged for at cost. We will be glad to send you a booklet if you are at all interested.

ROSS K. CHILDHEROSE, M.D.
Associate Physician

WILLIAM DEVITT, M.D.
*Superintendent and
Physician in Charge*

New Lea & Febiger Books

See These Works at Chicago—Booth 52

NEW WORKS

DIETETICS FOR THE CLINICIAN

By MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P. Four hundred pages are devoted to the dietetic indications of over one hundred common diseases, with menus for three days. Octavo, 666 pages. Cloth, \$6.50, net.

ALLERGY IN GENERAL PRACTICE

By SAMUEL M. FEINBERG, M.D., F.A.C.P. A book for the general practitioner, more practical, direct and guiding, and less encyclopedic than any yet published. Octavo, 339 pages, illustrated with 23 engravings and a colored plate. Cloth, \$4.50, net.

METABOLIC DISEASES AND THEIR TREATMENT

By DR. ERICH GRAFE. This work, by an authority of world-wide reputation, offers a condensed and simplified discussion largely confined to treatment. Octavo, 551 pages, illustrated with 37 engravings. Cloth, \$6.50, net.

INTERNAL MEDICINE. Its Theory and Practice

By Eminent Contributors. Edited by JOHN H. MUSSER, M.D., F.A.C.P. Well organized, absolutely authoritative, and a useful and efficient source of ready reference. Octavo, 1316 pages, illustrated. Cloth, \$10.00, net.

A TEXT-BOOK OF NEUROPATHOLOGY

By ARTHUR WEIL, M.D. Covering the entire subject, including every recent advance, and summarizing the facts hitherto scattered throughout the literature. Octavo, 335 pages, illustrated with 260 engravings. Cloth, \$5.00, net.

NEW EDITIONS

CALCIUM METABOLISM AND CALCIUM THERAPY

By ABRAHAM CANTAROW, M.D. Thoroughly revised to include the rapidly accumulating knowledge in this field and establishing calcium therapy on a rational basis. Second edition, thoroughly revised. 12mo, 252 pages, illustrated. Limp binding, \$2.50, net.

HYPERTENSION AND NEPHRITIS

By ARTHUR M. FISHBERG, M.D. Revised and enlarged to cover the latest methods of diagnosis and treatment. Third edition, thoroughly revised. Octavo, 668 pages, illustrated with 39 engravings and a colored plate. Cloth, \$6.50, net.

INFECTIONS OF THE HAND

By ALLEN B. KANAHEL, M.D. Covering the author's recent experience, study and research, including the anatomy, pathology and treatment of infections. Sixth edition, enlarged and thoroughly revised. Octavo, 552 pages, illustrated with 216 engravings, some in colors and a colored frontispiece. Cloth, \$6.00, net.

LABORATORY MEDICINE. A Guide for Students and Practitioners

By DANIEL NICHOLSON, M.D. Greatly enlarged and thoroughly revised to provide fully detailed information on the indications, methods and interpretations of the most important tests. Second edition, thoroughly revised and much enlarged. Octavo, 566 pages, illustrated with 124 engravings and 3 colored plates. Cloth, \$6.50, net.

PATHOGENIC MICROORGANISMS

By WILLIAM H. PARK, M.D., and ANNA WESSELS WILLIAMS, M.D. Revised and enlarged to include every advance in the field, based on the experience of these prominent authorities. Tenth edition, enlarged and thoroughly revised. Octavo, 867 pages, illustrated with 215 engravings and 11 full-page plates. Cloth, \$7.00, net.

STARLING'S PRINCIPLES OF HUMAN PHYSIOLOGY

Edited and Revised by C. LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., and H. HARTRIDGE, M.A., M.D., Sc.D., F.R.S. Including for the first time references to the literature and covering all of the extensive new knowledge. Sixth edition, enlarged and revised. Octavo, 1122 pages, illustrated with 562 engravings, 10 in color. Cloth, \$8.75, net.

LEA & FEBIGER



600 Washington Square
PHILADELPHIA, PA.

Please send me:

☐ Bridges..... \$6.50
☐ Feinberg..... 4.50
☐ Grafe..... 6.50
☐ Mussler..... 10.00

☐ Weil..... \$5.00
☐ Cantarow..... 2.50
☐ Fishberg..... 6.50
☐ Nicholson..... 6.50

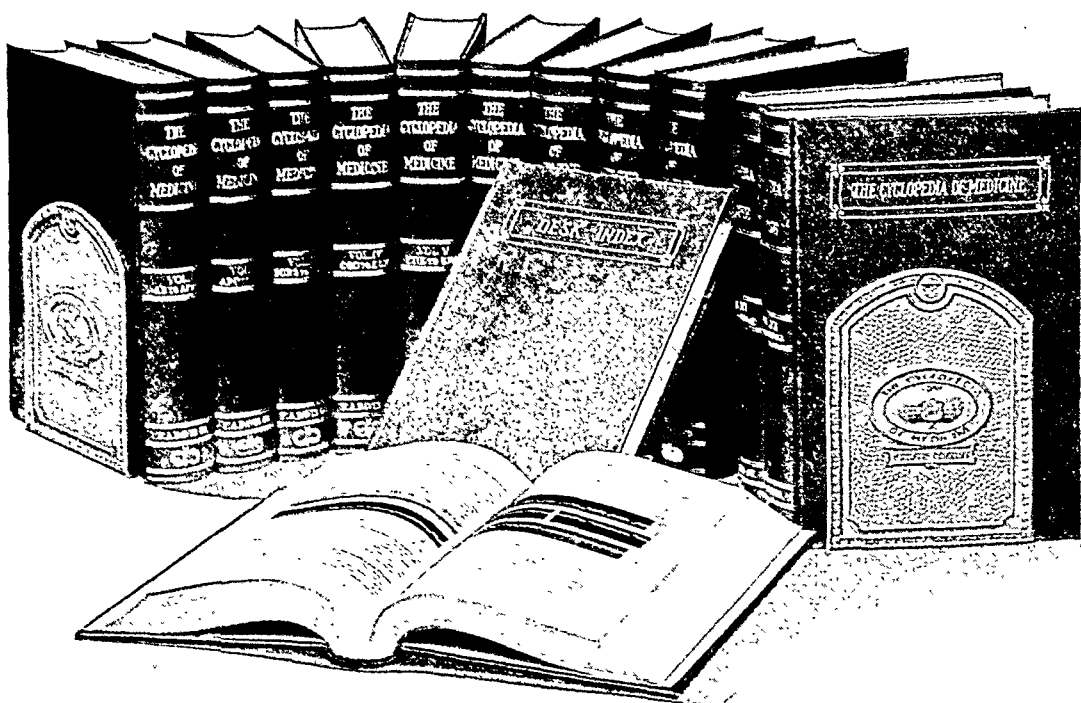
☐ Kanavel..... \$6.00
☐ Park & Williams.. 7.00
☐ Starling..... 8.75
☐ Catalogue

Name.....

A. S. L. M. 3 341

Address.....

Please Mention this Journal when writing to Advertisers



THE CYCLOPEDIA OF MEDICINE

GEORGE MORRIS PIERSOL
Editor-in-Chief

EDWARD L. BORTZ
Assistant Editor

Chief Associate Editors

W. Wayne Babcock Conrad Berens
P. Brooke Bland A. Graeme Mitchell
Francis L. Lederer

Associate Editors

Franklin C. Bing	F. S. Hammett
Harry L. Bockus	H. J. John
Claude P. Brown	John B. Ludy
W. Emory Burnett	John Royal Moore
A. F. Coca	Victor C. Myers
D. deRivas	Clarence A. Patten
John S. Coulter	P. S. Pelouze
Temple Fay	Eugene P. Pendergrass
Arthur First	Stanley P. Reimann
Philip Halper	William D. Stroud

and 700 Contributors

NOT A SYSTEM—

But a practical library of the medical sciences composed of monographs by outstanding authorities in medicine, surgery and the specialties, published in cyclopedic form both for the convenience and economy of the profession.

Judging by the increasing number of orders for the Cyclopedia and the many enthusiastic letters of approval that are being received by the editors, we have at last produced the ideal reference library for the specialist and practitioner.

ALWAYS UP TO DATE
SUPPLEMENTED ANNUALLY

"I desire to congratulate you on the excellence of your Cyclopedia of Medicine. It is the work of art from the printing and publishing viewpoint and its literary and scientific excellence is unexcelled in any publication that I have seen."

Seale Harris, M.D.

F. A. DAVIS COMPANY
1914-16 CHERRY STREET
PHILADELPHIA

Please send me complete descriptive material about The Cyclopedia of Medicine.

Name

Address

For **20** Years

HAY FEVER

has been prevented

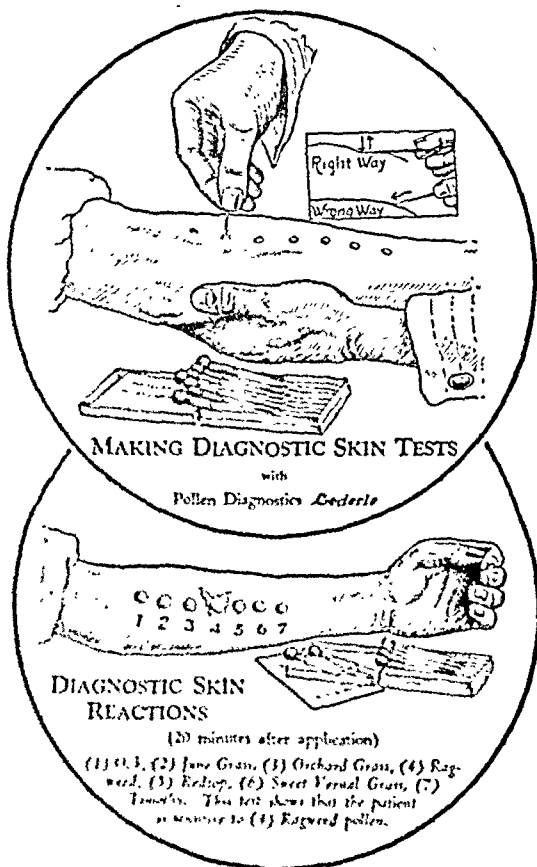
in thousands of cases

with

Pollen Antigen

Lederle

INTRODUCED BY LEDERLE LABORATORIES IN 1914



DIAGNOSIS OF HAY FEVER

With the Lederle Diagnostic Pollen Tests the diagnosis may be made in your office or in the patient's home.

A positive reaction occurring with a pollen to which the patient is known to be exposed when he is having Hay Fever indicates the Pollen Antigen to be used in desensitizing the patient.

The test is easily performed, accurate and safe.

GLYCEROLATED POLLEN ANTIGENS in stable and standardized solutions provide the general practitioner with a means for the scientific treatment of his Hay Fever patients. Each year has added evidence to the value of these solutions in the prevention and relief from symptoms of Hay Fever and each year an increasing number of physicians have familiarized themselves with the Hay Fever problem and are relieving their patients' attacks.

Literature upon request.

**LEDERLE LABORATORIES
INCORPORATED**

511 FIFTH AVENUE, NEW YORK

Please Mention this Journal when writing to Advertisers

A Safeguard for the Diabetic

INSULIN-STEARN'S

*A Constant, Unvarying
Therapeutic Factor*

The dosage of Insulin must be attuned to the needs of the patient. This means careful calculation on your part, careful observation, until the correct formula is reached.

Insulin-Stearns satisfies every requirement.

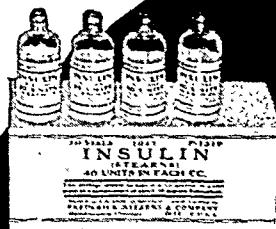
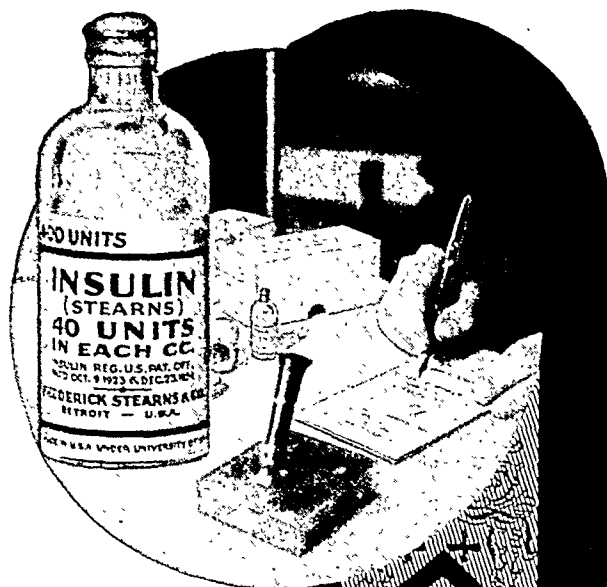
Manufactured in a special plant fitted with the latest in modern equipment, prepared under specialized control, Insulin-Stearns is always:

Biologically exact in potency

Remarkably clear

**Notably free from sting at
point of injection**

Let us send you complete literature describing Insulin-Stearns—how it is made, how it is supplied and recommended for use in actual practice. The facilities of Stearns Insulin Research Department are always at your service.



FREDERICK STEARN'S & COMPANY
DETROIT, MICHIGAN, U. S. A.

FREDERICK STEARN'S & COMPANY, Detroit, Michigan

A.I.M. 3

Gentlemen: I will be glad to have complete literature describing Insulin-Stearns.

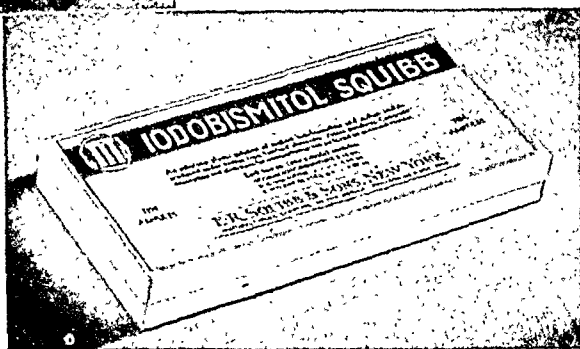
Doctor

Address City State

*An anti-syphilitic agent which
presents bismuth in
anionic form*



**IODOBISMITOL
SQUIBB**



LABORATORY tests of various bismuth preparations used in anti-syphilitic therapy have demonstrated that Iodobismitol differs from others in that its bismuth is largely in anionic form.

Iodobismitol may be used alone—in any stage of syphilis—or as an adjunct to the arsphenamines. Repeated doses are well tolerated by the kidneys and by the muscle into which it is injected.

Hanzlik (*J. A. M. A.*—98:537, 1932) has reported the presence of

bismuth in the spinal fluid of 47 out of 57 patients to whom Iodobismitol was administered.

Iodobismitol is a stable solution of sodium iodobismuthite (0.06 Gm. per cc.) in ethylene glycol containing 12% sodium iodide. It is obtainable under the Squibb label and is supplied in boxes of 10 and 100 2-cc. ampuls, and in 50-cc. vials.

E. R. SQUIBB & SONS, NEW YORK
MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858.

From the diary of the original Samuel Pepys:

Feb. 21, 1665. And then my wife being busy in going with her woman to a hot-house to bathe herself, after her long being within doors in the dirt, so that she now pretends to a resolution of being hereafter very clean. How long it will hold I can guess.

An apology for Mrs. Samuel Pepys

MRS. PEPYS did not take many baths—but no one did in the 17th Century.

Cold houses, lack of even tub-and-sponge facilities, made bathing an ordeal. The desirability of cleanliness was recognized, as Pepys' comment indicates—but the *practice* of cleanliness did not begin until bathing was made *pleasanter*.

Parke-Davis has applied much the same reasoning to vitamin therapy—*i. e.*, by making vitamin therapy pleasanter, its field can be substantially broadened. And to make it pleasanter, you have Parke-Davis Haliver Oil products.

It is a well-known fact that adults are more squeamish than children about taking cod-liver oil, and preparations containing it. Their aversion to fish oil is completely obviated by the high potency of Haliver Oil. All the adult patient has to do is to take one

or two tiny tasteless capsules, instead of those distasteful teaspoonfuls.

When vitamins A and D are needed, prescribe Parke-Davis Haliver Oil. Because it's pleasanter, you'll have the satisfaction of knowing that your treatment is being followed. And this holds true for children as well as adults.

Parke-Davis Haliver Oil (either Plain or with Viosterol-250 D and in bottle or capsule form) is available at practically all drug stores in the United States and Canada.

HALIVER OIL WITH VIOSTEROL-250 D
Containing 32,000 vitamin A units (U. S. P. X.) and 3,333 vitamin D units (Steenbock) per gram.
HALIVER OIL PLAIN
32,000 vitamin A units (U. S. P. X.) and 200 vitamin D units (Steenbock) per gram.

PARKE, DAVIS & COMPANY
DETROIT, MICHIGAN

*The World's Largest Makers
of Pharmaceutical and Biological Products*

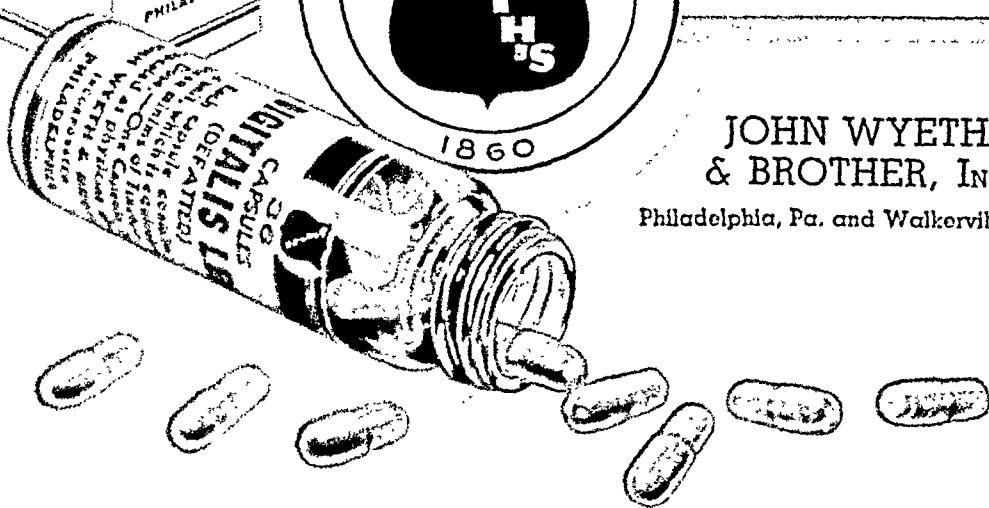
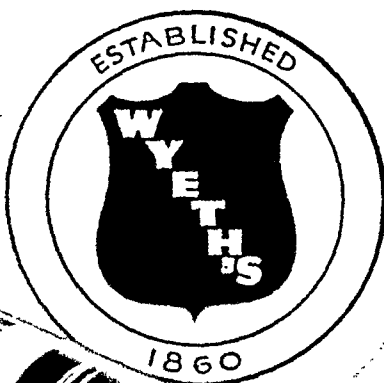
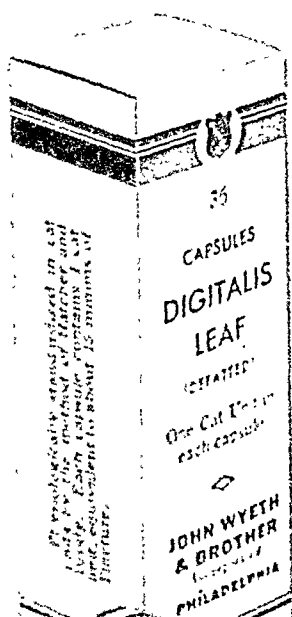
Replacing the Medicine Dropper

In digitalis medication, where accuracy of dosage is essential, the use of the medicine dropper by the patient for measuring dosage is often inadvisable.

You will thus appreciate Wyeth's Capsules Digitalis Leaf (Defatted) for accuracy of dosage, convenience and uniformity. They offer several decided advantages, regardless of individual preferences as to methods of standardization:

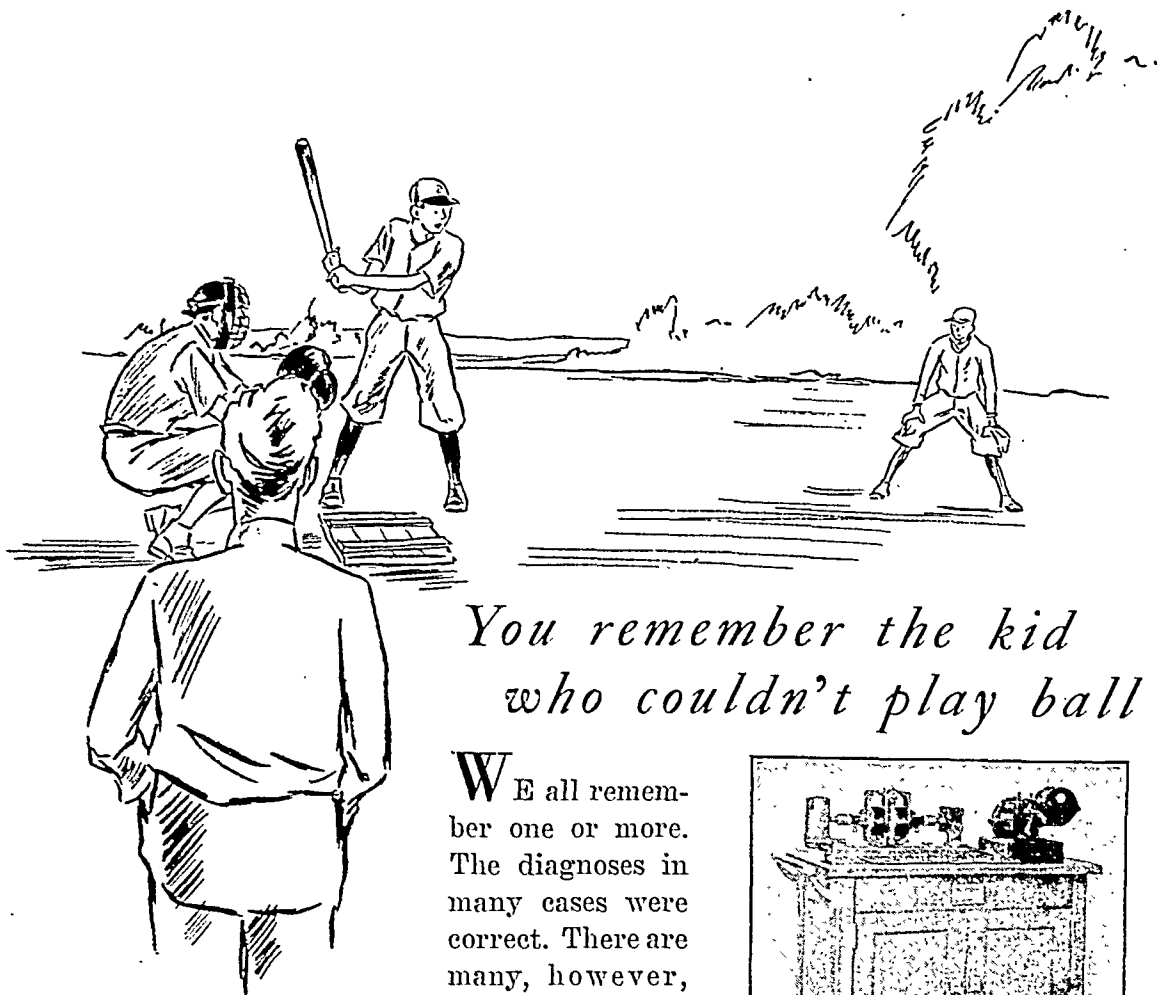
1. Dependable activity of the drug.
2. Unvarying quantity of digitalis in each capsule.
3. Each capsule represents: 15 minims of Tincture Digitalis U. S. P. or 1 Cat Unit (Hatcher and Brody).
4. Doubly Standardized—Assayed by both the U. S. P. Frog Method and the Cat Method of Hatcher and Brody.
5. Convenient—Obviates discrepancies between minims and drops, and avoids the use of household measuring devices.

Supplied in vials of 36 capsules (sufficient for average digitalization).



**JOHN WYETH
& BROTHER, INC.**

Philadelphia, Pa. and Walkerville, Ont.



*You remember the kid
who couldn't play ball*

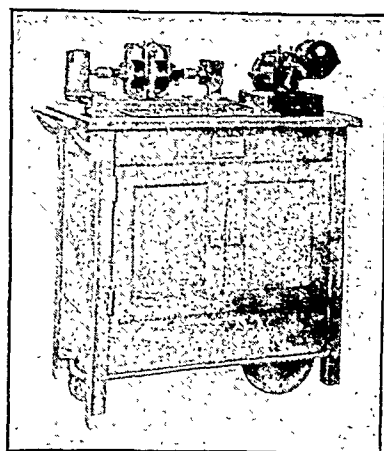
WE all remember one or more. The diagnoses in many cases were correct. There are many, however, who could have

safely grown to be professional baseball players or ladder climbers for the fire department. Without the electrocardiograph, arrhythmias, normal to the growing heart, may be readily mistaken for serious disturbances. The accuracy and certainty of diagnoses based upon electrocardiograms warrant their use in all cases involving the heart of young and old alike.

"Pioneer Manufacturers of the Electrocardiograph"

**CAMBRIDGE
INSTRUMENT CO INC**

3732 Grand Central Terminal, New York City



The Hindle "all-electrics" are made in portable as well as in mobile and stationary types. They are accurate, rugged and simple to operate and suitable for office, clinical and hospital use.

Literature sent upon request

H I N D L E
"ALL-ELECTRIC"
ELECTROCARDIOGRAPH

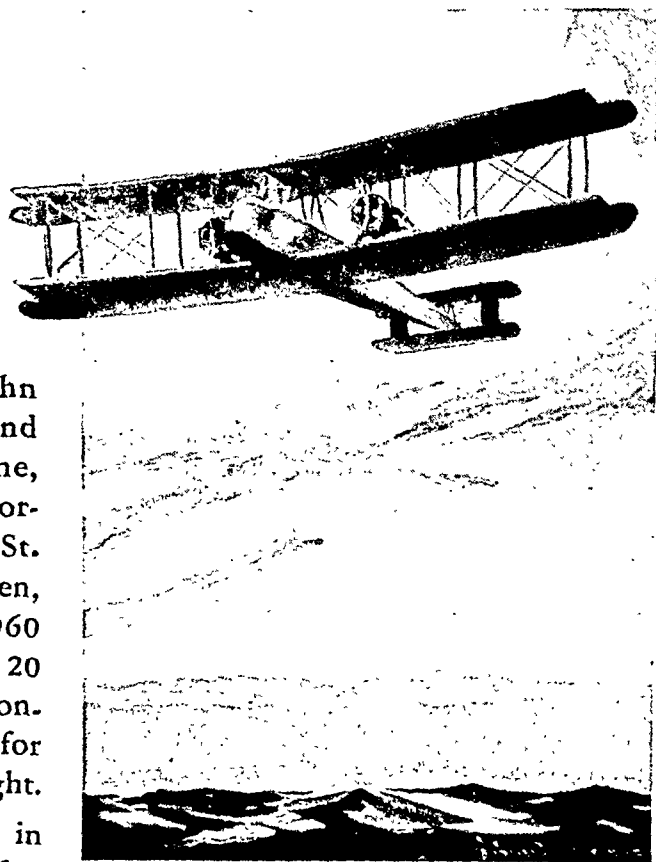
IMPORTANT EVENTS of 1919

First non-stop flight across Atlantic

June 15, 1919. Captain John Alcock, English navigator, and Lieutenant Arthur W. Browne, American, flew in their twin-motored Vickers-Vimy plane from St. Johns, Newfoundland, to Clifden, Galway, Ireland, spanning 1960 miles of ocean in 16 hours and 20 minutes, thereby winning the London Daily Mail prize of \$50,000 for first non-stop trans-Atlantic flight.

Another noteworthy happening in 1919 was the publication of Professor Dercum's article, which heralded a radical change in the treatment of epilepsy in this country - - Luminal in place of bromides.

Since then the value of Luminal in this disease, as well as in various neuroses and other conditions requiring a potent sedative, antispasmodic or hypnotic, has been generally recognized by the American medical profession, as attested by hundreds of published reports.



When the physician prescribes Luminal he has the assurance of high chemical purity and uniformity of composition. For many years its synthetic production has been supervised by the same expert and experienced chemists in the same factories located at Rensselaer, New York.

Thus there are good and substantial reasons for specifying Luminal in your prescription.

LUMINAL

REG. U. S. PAT. OFF. & CANADA
Brand of PHENOBARBITAL

*Write for literature containing detailed information and
dosage on the use of Luminal in the various indications.*



WINTHROP CHEMICAL COMPANY, INC., NEW YORK, N. Y.

Laboratories and Factory: RENSSELAER, N. Y.

*Visit the Winthrop-Metz exhibit No. 41 at the American College of Physicians convention.
Representatives will be on hand to welcome you and give you particulars
on various Winthrop and Metz preparations.*

307M

Please Mention this Journal when writing to Advertisers

THE *Importance of Vitamins* IN THE DIETARY

THE increasing recognition of the importance of vitamins in the dietary, has focused undue attention upon specific vitamins, and less upon others of equal importance. It is but natural that those sponsoring a product having a high potency of any single vitamin should stress the value of that one above all others.

But medical research has demonstrated that it is becoming increasingly difficult to separate, definitely, the functions of one vitamin from those of another. For example, investigation appears to show that vitamin D, associated with calcium and phosphorus, tends to prevent dental caries. It also appears that vitamin C is likewise of value in the prevention of tooth decay. It has been shown that an excess of vitamin D increases the tendency to infection unless the ingestion of vitamin A is correspondingly increased. Research has indicated that not only vitamin A but also vitamins B and G are growth promoting. In a word, the sympathetic unity of action of vitamins must have the physician's consideration.

Further, it has been shown that there exists a definite balance between vitamins;

by greatly increasing vitamins A and D in diets, an otherwise adequate amount of vitamin B is made inadequate—leading to death of animals. Care should be taken not to overdose with cod liver oil or viosterol unless, at the same time, an increasing quantity of vitamins B and G are also added to the diet. As a result of new information, there is a growing tendency on the part of the medical profession to advocate the administration of vitamins in group form.

Maltine With Cod Liver Oil provides a generous amount of four vitamins—A, B, D and G—in one palatable, nutritive combination. 70% is Maltine, a concentrated fluid extract of the nourishing elements of malted barley, wheat and oats—rich sources of vitamins B and G. 30% is pure, vitamin-tested cod liver oil—of high potency in vitamins A and D. Taken with orange or tomato juice vitamin C is added. *Maltine With Cod Liver Oil is biologically standardized and guaranteed to contain vitamins A, B, D and G.* Biological and vitamin report on request. The Maltine Company, Established 1875. 30 Vesey Street, New York, N. Y.

This Trade-mark Identifies the Only Genuine

Maltine

Reg. U. S. Pat. Off.

WITH COD LIVER OIL—Introduced in 1875



Member NRA
We do our part

Calcium-Phosphorus Deficiencies IN DENTAL CARIES

THE *Annual Review of Biochemistry*, 1932, cites as among the more important developments in biochemistry for 1931 studies attesting the clinical value of vitamin D in arresting dental caries.¹

"Clinical trials of the value of vitamin D in arresting dental decay in children have been strikingly successful," the report states further.

Many theories have been put forth concerning the etiology of dental caries, but since it is recognized that the composition of teeth is largely calcium and phosphorus and that the tooth has a circulatory system, it is logical to suppose that the calcifying factor, vitamin D, is essential for sound tooth structure.

Vitosterol for Arrest of Caries

Recent studies point especially to the efficacy of viosterol in dental prophylaxis. A 24-year study of 800 English children receiving various dietary additions showed irradiated ergosterol to be of striking value in arresting dental caries, the rate of spread of caries being only one-third that of the control group.²

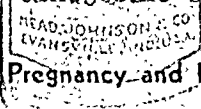
Write for new literature, "The Dental Value of Vitamin D in Pregnancy and Lactation."

Price,³ Boyd and Drain,⁴ Davis,⁵ and the Toveruds⁶ are among the numerous other authorities whose clinical studies reveal that vitamin D improves tooth structure or inhibits decay.

Vitamin D for Adults

McCollum, referring to studies by himself and associates, states, "Decay, we believe, is the result, in most instances, of a diet unsatisfactory in respect to its calcium, phosphorus and vitamin D content."

Speaking of Mellanby's work, he continues, "Her results harmonize with our interpretation that a dietary regimen which tends to maintain the phosphorus and calcium of the blood at a high level tends to render the individual caries-immune. . . I believe no one alert to existing knowledge would hesitate now to state unqualifiedly that the pregnant and nursing mothers of today are getting too little vitamin D. If our studies and those of Mrs. Mellanby are as sound as we believe they are, they will afford evidence that in temperate regions people of all ages should take some source of vitamin D."



MEAD'S CEREAL *

ENRICHED WITH MINERAL AND
VITAMIN CONTAINING FOODS

SUPPLIES Calcium and Phosphorus

This tasty food contains 6 times more calcium than fluid milk, formerly one of the best sources of this mineral. Two ounces of Mead's Cereal alone supplies the adult's daily minimum requirement of 0.45 Gm. Ca. In addition, Mead's Cereal is richer in phosphorus than the principal foodstuffs. For sale at drug stores, in 1- and 4-lb. packages.

1-7 Bibliography on request.

MEAD'S VIOSTEROL

in Oil 250 D

UTILIZES Calcium and Phosphorus

Mead's Viosterol maintains serum calcium and phosphorus in proper ratio and enables the body to store these minerals in bones and teeth. It is the most potent type of vitamin D product commercially available. It is offered as a dental prophylactic of utmost purity and uniform potency. Packed in brown bottles and light-proof cartons.

MEAD JOHNSON & CO., Evansville, Ind., *Pioneers in Vitamin Research*

* Now also supplied in pre-cooked form, as PANLUM. Dried, ready to serve by simply stirring (with a fork) with water or milk, hot or cold. Completely prepared in the cereal bowl in a few moments.

Please Mention this Journal when writing to Advertisers

ANNALS OF INTERNAL MEDICINE

VOLUME 7

MARCH, 1934

NUMBER 9

THE SIGNIFICANCE OF THE HYPERTROPHY AND HYPERPLASIA OF THE PARATHYROID GLANDS IN RICKETS AND OSTEOMALACIA *

By RUSSELL M. WILDER, M.D., GEORGE M. HIGGINS, PH.D., and CHARLES
SHEARD, PH.D., *Rochester, Minnesota*

THE earliest suggestion of a correlation between the function of the parathyroid glands and rickets is to be found in a contribution of Erdheim² in 1906. Extirpation of the parathyroid glands of young rats led to decalcification of the dentin of the incisor teeth and to dental abnormalities resembling those found in spontaneous rickets of rats. In the normal rats, after parathyroidectomy, an increased amount of osteoid tissue developed, especially in the ribs; fractures occurred and the deposit of calcium in the calluses of the fractures was deficient. A cartilage typical of rickets was not seen, but this discrepancy was explained by retarded growth, and it was Erdheim's opinion that parathyroid deficiency leads to disturbances of ossification which are essentially the same as those of rickets.^{4,5} He had observed, in the meantime, enlargement of the parathyroid glands in cases of osteomalacia³ of man, as well as in two cases of late rickets of human beings, and thus he arrived at the conclusion that the parathyroid glands must be inadequate at the time of onset of these conditions. The calcium-impooverishment in rickets, like that which follows parathyroidectomy, indicated, for him, a failure of parathyroid function, and the enlargement of the parathyroid glands, as observed in osteomalacia and rickets, an attempt at compensation. It should be recalled that these observations and conclusions antedated the discovery of vitamin D, and that the etiology of these skeletal diseases at that time was a matter of conjecture.

Others were quick to confirm Erdheim's finding of enlargement of parathyroid glands in osteomalacia, but his conclusions encountered some opposition for the reason that gross enlargement of these glands was not found in infantile rickets, either by himself or others. He explained it on the ground that a large majority of infants suffer from rickets, so that criteria regarding the size of perfectly normal infantile parathyroid glands were

* Read before the Central Society for Clinical Research, Chicago, Illinois, October 27, 1933.

From the Division of Medicine, Division of Experimental Medicine, and the Division of Physics and Biophysical Research, The Mayo Clinic and The Mayo Foundation.

lacking. This matter is still unsettled, but since then it has been conclusively demonstrated by Nonidez and Goodale¹⁶ and Higgins and Sheard¹⁰ that deprivation of vitamin D, in chickens, not only produces rickets, but is regularly accompanied by very evident hypertrophy and hyperplasia and gross enlargement of the parathyroid glands. The consistency of this is such as to suggest a direct correlation between the demand for the parathyroid product and the availability of vitamin D, a correlation which we believe to have been further elucidated by experiments to be described.

The terms "hypertrophy" and "hyperplasia" are so frequently mis-handled as to make it necessary to define the usage intended. Hypertrophy is applied, by us, to an increase in the size of the individual epithelial cells of the organs in question and hyperplasia to an obvious increase in the number of these cells. Enlargement of the glands may result from either hypertrophy or hyperplasia, or from both, or from some such pathologic process as cyst formation, with or without hypertrophy, or hyperplasia.

The majority of those interested in rickets and osteomalacia have accepted Erdheim's opinion that the parathyroid enlargement of osteomalacia is an index of increased parathyroid function, but no proof for this has been submitted, and others, notably Klemperer,¹³ have considered that the enlarged glands are actually depressed in function, "a fruitless attempt to compensate for calcium deficiency." It seemed to us that this question could be settled very simply. Parathyroid hormone could be administered to chicks deprived of vitamin D, and if, as supposed, the hypertrophy and hyperplasia of parathyroid glands resulting from deficiency of vitamin D is an index of increased demand for parathyroid product, the supplying of the product by injection might prevent the development of these abnormalities. Experiments of this nature might also reveal to what extent the parathyroid product would compensate for deficiency of vitamin D.

EXPERIMENT 1 *

Six week old chicks from the same hatching of the eggs of one flock of pure bred White Leghorn hens received diets containing 2 per cent of a crude commercial cod liver oil. This had not been assayed for vitamin potency (table 1). The season was midwinter and the pens were situated

TABLE I
Chicken Diet for Experiment 1

Yellow corn meal.....	56
Wheat middlings.....	18
Powdered buttermilk.....	18
Salt.....	1
Sand grits.....	5
Cod liver oil.....	2
Calcium by analysis.....	0.45 per cent
Phosphorus by analysis.....	0.48 per cent

* The results of this earlier experiment were the subject of a preliminary report. Higgins, Sheard and Wilder: Proc. Staff Meet., Mayo Clinic, 1932, vii, 311-313.

behind windows of ordinary glass so that the amount of ultra-violet radiation was reduced to a minimum. Thus the cod liver oil was the only important source of vitamin D.

The birds were divided among six pens, A to F, two males and two females to a pen. The diet in pens C, D and F was supplemented with 5 per cent of bone ash which proved to be without significance. The birds in pens A and C were injected daily with 0.8 unit of parathormone (Lilly) for each 100 gm. of body weight; those in pens B and D received, in the same manner, 1.6 units for each 100 gm. of body weight. These injections were continued for six weeks. All of the birds thrived. The curves of the weight changes with and without parathormone were essentially alike. Roentgenograms gave no evidence at any time of any changes in the bones, and the values for serum calcium were normal throughout (table 2).

TABLE II

Serum Calcium and Phosphorus Values of Chicks at Close of Experiment 1

Pen	Calcium, mg. per cent	Phosphorus, mg. per cent
A*.....	13.27	5.78
B*.....	13.87	5.86
C*.....	13.17	5.76
D*.....	12.88	5.52
E.....	12.74	5.59
F.....	13.05	5.71

* The birds in pens A, B, C and D received daily injections of parathormone (Lilly).

However, in all the chicks in pens E and F to which no parathormone had been given, with one exception, there was some degree of abnormality in the parathyroid glands. It ranged from simple hypertrophy to frank hyperplasia. In many cases the glands were several times as large as normal and contained cysts. The abnormality was unrelated in degree to the amount of calcium in the diet. It was less intense, but otherwise entirely like that previously described by Higgins and Sheard for chicks deprived of vitamin D.

In contrast to the pathologic appearance of the parathyroid glands of the control birds, the parathyroid glands of the chicks which received parathormone were normal in appearance, both grossly and pathologically. It was concluded that the crude cod liver oil in the diet provided a relatively inadequate supply of vitamin D.* Rickets was prevented by this small amount of vitamin D, but not the hypertrophy and hyperplasia of the parathyroid glands, and, since administering parathormone medicinally had prevented alteration of the glands, it seemed reasonable to infer that the glands of the untreated chicks had been called on to deliver a larger than normal supply of hormone which in turn had resulted in their compensatory hypertrophy and hyperplasia.

* This conclusion is confirmed by the absence of alterations of the parathyroid glands in control experiment B (page 1065).

Experiment 1 had been designed with quite another objective. We were aiming at the production in chicks of the fibrous osteosis of hyperparathyroidism, such as had been obtained in rats, guinea pigs and puppies by Jaffé and his associates and by Johnson¹² and Wilder. This failed. The chick has proved highly resistant to injections of parathormone. The observation that parathormone prevented hypertrophy and hyperplasia of the parathyroid glands was accidental. It prompted our undertaking the following experiments in which chicks were more rigidly deprived of vitamin D.

EXPERIMENT 2

A flock of 36, ten day old White Leghorn chicks from one hatching of the eggs of one flock of pure bred hens, was placed behind amber glass* and the birds were given a ration greatly deficient in vitamin D and relatively poor in calcium and phosphorus. It was essentially the same as the diet of experiment 1 (table 1) but the cod liver oil was omitted.

One group of these birds, 24 in number, was treated from the beginning with 0.8 unit of parathormone for each 100 gm. of body weight. This was injected daily, subcutaneously.

The calcium and phosphorus values of the blood serum of a few individuals of both the treated and the untreated groups are given below (table 3). No significant differences are observable in these; the value for calcium

TABLE III
Serum Calcium and Phosphorus Values of Chicks at Close of Experiment 2

Calcium, mg. per cent	Phosphorus, mg. per cent
8.47	6.06
6.11	6.12
5.91	6.25
6.90 *	4.63 *
5.52 *	6.61 *

* Values followed by an asterisk were obtained in individual birds treated with parathormone; values not so designated were obtained in individual birds of the untreated group. All the birds gave clear evidence of rickets.

is low in both groups. However, the degree of rickets in the birds treated with parathormone was somewhat less, and also the group thus treated with parathormone had gained an average of 135 gm. as compared to 108 gm. in the untreated group (table 4). The parathyroid glands in both groups revealed hypertrophy and hyperplasia but these processes were less prominent in the treated birds.

Ten of the parathyroid-treated birds from experiment 2 which had not been killed at the end of that experiment, were placed on a diet in which meat scraps replaced the dried buttermilk of the previous diet. Particles of bone in the meat scraps raised the values for calcium and phosphorus (table 5). The sand grit was also increased. In half of this flock the

* Pyrex glass No. 54, as used previously by Higgins and Sheard.

TABLE IV
Average Weights of Chicks in Experiment 2

Date, 1932	Birds receiving parathormone, 0.8 unit per 100 gm. weight, gm.	Birds receiving no parathormone, gm.
6-28.....	90	96
7- 5.....	144	126
7-11.....	183	154
7-18.....	201	185
7-25.....	225	204

All birds were rigidly deprived of vitamin D. They were 10 days old 6/28/32.

TABLE V
Diet of Birds in Experiment 3

Food	
Yellow corn meal.....	58
Wheat middlings.....	18
Meat scraps containing bone.....	18
Salt.....	1
Sand grits.....	10
	<hr/> 105
Calcium by analysis.....	1.44 per cent
Phosphorus by analysis.....	0.93 per cent

previous treatment with parathormone was continued as before; in the other half, it was discontinued. After 11 days on this regimen all the birds were killed.

During life, no difference was apparent between the birds that continued to receive parathormone and those that had received no further treatment. The value for serum calcium remained low in both groups. Examinations of the parathyroid glands, however, revealed smaller glands in the birds that had continued on the parathormone and less evident hypertrophy and hyperplasia.

EXPERIMENT 4

A group of 15, four week old chicks from a hatching of eggs from a flock of Brown Leghorn hens, was placed behind amber glass and given the diet recorded under experiment 3 (table 5). Six birds of this flock were treated with parathormone in a dosage of 0.8 unit daily for each 100 gm. of body weight. The remainder received no parathormone.

A significant difference was noted in the growth of these two groups, although rickets developed in both. After eight weeks (the chicks now being 12 weeks old) all the birds were killed for examination. At this time the treated birds had increased in weight an average of 297 gm. as compared to 207 gm. for the untreated birds (table 6). The parathyroid glands were hypertrophic and hyperplastic in both groups but these changes were less marked in the treated birds.

TABLE VI
Average Weights of Chicks in Experiment 4

Date, 1932	Birds receiving parathormone, 0.8 unit per 100 gm. weight, gm.	Birds receiving no parathormone, gm.
8- 1.....	231	213
8- 8.....	279	237
8-15.....	321	291
8-22.....	339	
8-29.....	408	345
9- 5.....	432	360
9-12.....	456	360
9-19.....	504	360
9-26.....	528	420

All birds were rigidly deprived of vitamin D. They were 28 days old 8/1/32.

CONTROL EXPERIMENT A

Twelve chicks, ten days old, from the same hatching as those used in experiments 2 and 3 were placed behind "vitaglass," which transmits ultra-violet light, and were fed the diet of experiment 3 (table 5). One-half of this flock received daily subcutaneous injections of parathormone in the same dosage used in experiments 2 and 3. There was no rickets and after 12 weeks, direct and microscopic examination of the bones revealed no abnormalities. The parathyroid glands of the treated birds showed some evidence of involution in the form of a fibroblastic invasion. The values for serum calcium and serum phosphorus were normal in both groups. The growth was somewhat less rapid in the birds treated with parathormone than in the birds not so treated (table 7). This result is exactly the opposite of that obtained with birds deprived of vitamin D, as in experiment 2.

TABLE VII
Average Weights of Chicks in Control Experiment A

Date, 1932	Birds receiving parathormone, 0.8 unit per 100 gm. weight, gm.	Birds receiving no parathormone, gm.
6-28...	90	90
7- 5...	144	141
7-11...	168	210
7-18...	208	243
7-25...	255	279
8- 1...	330	390
8- 8...	424	498
8-15...	552	624
8-22...	648	720
8-29...	720	816
9- 5...	780	816
9-12...	780	900
9-19...	780	1110
9-26...	840	1278

Birds all under vitaglass, thus supplied with vitamin D. Diet same as in experiment 3. Birds were 10 days old 6/28/32.

CONTROL EXPERIMENT B

Twelve chicks, four weeks old, from the same hatching as those used in experiment 4, were placed behind amber glass and received the diet used in experiments 3 and 4 (table 5) but supplemented by 3 per cent of crude commercial cod liver oil. Half of this flock was given daily injections of parathormone in the same dosage used in experiment 4. No weakness of the legs was apparent. Growth was practically the same in both groups (table 8). Treatment with parathormone neither increased it, as in the

TABLE VIII
Average Weights of Chicks in Control Experiment B

Date, 1932	Birds receiving parathormone, 0.8 unit per 100 gm. weight, gm.	Birds receiving no parathormone, gm.
8- 1.....	279	234
8- 8.....	321	255
8-15.....	381	291
8-22.....	471	441
8-29.....	561	441
9- 5.....	564	513
9-12.....	648	618
9-19.....	720	687
9-26.....	768	771

Birds all under amber glass receiving the diet used in experiment 4 but supplemented by 3 per cent of crude commercial cod liver oil. Birds 28 days old on 8/1/32.

case of the birds deprived of vitamin D, in experiment 4, nor decreased it as appeared in control experiment A.

After eight weeks the birds were killed for examination. The parathyroid glands of those which had received parathormone were rather markedly invaded with fibroblastic tissue suggesting functional involution. The glands of those not treated with parathormone appeared normal.

The bones of the birds treated with parathormone revealed, on microscopic examination, a slight but definite degree of lacunar resorption with replacement of cancellous structure by fibrous connective tissue. This is the first time in a large series of experiments that such evidence of fibrous osteosis has been obtained in the chick.

COMMENT

The following recapitulation of the evidence now at hand will simplify its interpretation:

Evidence for Increased Parathyroid Function in Conditions of Deficiency of Vitamin D. 1. The parathyroid glands of chicks deprived of vitamin D are consistently enlarged (Nonidez and Goodale, Higgins and Sheard).

2. Gross enlargement is frequently associated with cyst formation, but depends primarily on an increased size of the "chief" cells, hypertrophy, due to an increased amount of the cytoplasm of these cells. This is accom-

panied by an increase in the number of cells, hyperplasia (Higgins and Sheard).

3. Enlargement, hypertrophy and hyperplasia are roughly proportional to the severity of deprivation of vitamin D, moderate in experiment 1, much more marked in experiments 2 and 4.

4. Restoring vitamin D to chicks, previously deprived of this vitamin and suffering with florid rickets, not only causes the rickets to "heal," but is followed by early regression of the accompanying parathyroid abnormality. The glands not only diminish in size but the individual cells resume their normal size.*

5. The enlargement, hypertrophy and hyperplasia of the parathyroid glands in deficiency of vitamin D is counteracted by subcutaneous injections of parathormone. In experiment 1, in which the deprivation of vitamin was insufficient in degree to provoke rickets, the hypertrophy and hyperplasia were prevented by these injections. In experiments 2, 3 and 4 in which the deprivation of vitamin was more severe, there was still some evidence of inhibition in most cases.

Other evidence for increased parathyroid function in rickets has been reported by Hamilton and Schwartz.⁶ Calcium salts administered by mouth to normal rabbits increased the serum calcium to a very slight degree, but if normal rabbits were previously given injections of parathormone, the same dose of calcium usually caused death from hypercalcemia. Rachitic rabbits behaved in such experiments as the normal rabbits behaved which previously had been given injections of parathormone.

Evidence for a Compensation Effected by an Increased Secretion of the Parathyroid Product in Deficiency of Vitamin D. 1. The minor degree of deficiency of vitamin D, in experiment 1, provoked hypertrophy and hyperplasia of the parathyroid glands not accompanied by any of the more common skeletal lesions of rickets. It is inferred that the augmented supply of parathyroid product derived from these glands sufficed to prevent the development of rickets.

2. The more extreme degrees of the vitamin deficiency in experiments 2, 3 and 4 provoked rickets despite any compensatory action by the enlarged glands. The injection of parathormone under such circumstances diminished the degree of the rickets but did not prevent its development. The doses used were relatively large (0.8 unit per 100 gm. of body weight).

3. The growth of chicks deprived of vitamin D was favored by injections of parathormone in experiments 2 and 4, although when vitamin D was adequately supplied, as in control experiments A and B, no such growth-promoting effect was observable.

The evidence presented warrants the conclusion that the parathyroid glands are driven to increased functional activity by deficiency of vitamin D. It further reveals that increasing the supply of the hormone affords some protection against deficiency of the vitamin. It does not explain the nature

* Experiments reported elsewhere (Higgins, Sheard and Wilder¹¹).

of the protection afforded but other information now at hand bears directly on this question.

It is evident, in the first place, that the hormone does not directly replace the vitamin. In itself it has no vitamin D effect. Extra hormone, whether from hyperactive glands or supplied by injection of commercial hormone, prevents the development of rickets only when the deficiency of vitamin is relatively slight. Indeed the protection afforded by the hormone is directly proportional to the amount of vitamin D available. In experiment 1, in which the diet contained 2 per cent of crude cod liver oil, the protection afforded by the hormone was complete. In experiments 2, 3 and 4, with very rigid deficiency of vitamin D, the protection was unsatisfactory, but still in evidence. Presumably if the vitamin could be completely excluded no amount of hormone would protect at all.*

A second possibility, namely, that the hormone increases vitamin D effects by activating the vitamin, is unlikely. If it were true one would expect the potency of the commercial hormone to be the same, irrespective of the species of animal into which it is injected. It is not. Parathormone in doses of 1 unit per kilogram of body weight is noticeably active in man, whereas 20 times this dose given to normal chicks has little or no effect.

An explanation that seems to fit is the following: The hormone is not the vitamin, nor does it act like the vitamin, nor does it sensitize or activate the vitamin; its action is on the tissues of the organism which it sensitizes or conditions, so that the tissues can function normally with less vitamin than otherwise would be necessary. Support for this hypothesis is found in the following observations:

The discovery of Erdheim that parathyroidectomy is followed by decalcification of the dentin of the teeth of rats and failure to deposit calcium in the calluses of fractures, has been mentioned in the introduction. His interpretation of this observation, restated in the light of present day knowledge of the etiology of rickets, would be that a normally adequate supply of vitamin D becomes inadequate when the parathyroid hormone is removed. Hess and Lewis⁷ and later Hess, Weinstock and Rivkin^{8,9} reported the following: viosterol promptly raised the value for serum calcium in monkeys and dogs in which latent tetany was induced by deprivation of calcium, but after the parathyroid glands had been removed the value for serum calcium fell again and was then unaffected by doses of viosterol 40 times that which is prescribed for infants of equivalent weight. However, much larger doses of viosterol, in later experiments of Hess and his associates and according to Jones, Rapoport and Hughes[†] and Demole and Christ,¹ are effective even after parathyroidectomy. Kozelka^{14,15} has made a similar comment.

* Young chicks store a certain small amount of vitamin D, obtained presumably from the yolk of eggs from which they hatch. Complete deprivation of vitamin D is thus excluded as a possibility in experiments of this nature.

† It is an open question in all experiments of this kind, whether all existing parathyroid tissue has been resected. Accessory parathyroids are extremely difficult to uncover. It may be that in the absence of any parathyroid tissue whatsoever the organism would be quite insensitive to vitamin D.

Thyroparathyroidectomized dogs could be maintained free from tetany by giving vitamin D, but the doses required were several times as large as are normally required. In parturient animals several thousand rat units were used daily. Doses of this magnitude given to normal animals produce evidences of hypervitaminosis, as described by Hess and others. An abnormally high tolerance for vitamin D in parathyropriva is also apparent from the observations of Seeds and Reed.¹⁷

The other side of the picture is presented in observations of Johnson, working under the direction of one of us (Wilder), on the production in rats and puppies of the bony lesions of hyperparathyroidism. Johnson injected rats with parathormone in doses of from 2 to 20 units daily and uniformly produced the typical picture of parathyroid osteosis. Litter mates of these animals, receiving identical doses of parathormone, were given daily doses of 10 to 15 small drops of viosterol, representing not more than from 60 to 90 Steenbock units of vitamin D. In normal rats this dose of vitamin D was without noticeable toxic effect, but given with the parathormone it produced intense metastatic calcification of the kidneys. The conclusion to be drawn from these data must be that the sensitivity of an animal to vitamin D is decreased in parathyroid insufficiency and increased in conditions of parathyroid excess, which means, as stated in the hypothesis, that the hormone sensitizes the tissues of the organism to the action of the vitamin.

It may be asked whether the stimulus to the parathyroid glands in conditions of deficiency of vitamin D is the lack of vitamin, per se, or the resulting hypocalcemia. In experiment 1 the parathyroid glands became hypertrophic and hyperplastic in the presence of a normal value for serum calcium, which seems to point to a direct effect on the glands.

CONCLUSIONS

Experiments with chicks reveal that deprivation of vitamin D, insufficient in degree to cause rickets, will produce hypertrophy and hyperplasia of the parathyroid glands; that the parenteral administration of parathormone in such minor degrees of deprivation of vitamin D prevents this hypertrophy and hyperplasia, but that when the deprivation of vitamin D is extreme, so that rickets is clearly in evidence, administering parathormone may restrict but will not prevent the hypertrophy and hyperplasia of the glands.

It appears from this and other evidence cited that the hypertrophy and hyperplasia of the parathyroid glands of chicks, under conditions of deficiency of vitamin D, depend on their accelerated functional activity.

Other observations are interpreted to mean that the supply of parathyroid hormone determines the sensitivity of the organism to the action of vitamin D. A diminished supply of the hormone, as after parathyroidectomy, diminishes the ability of the organism to function normally with restricted amounts of vitamin D; an augmented supply conditions the tissues of the organism so that the effects of the vitamin are more intense, and so that

amounts of the vitamin which otherwise would not prevent rickets, do prevent rickets.

By virtue of the capacity of the parathyroid glands to accelerate the rate of supply of their product, and owing to the resulting conditioning of the tissue (increased sensitivity to vitamin D), the organism is enabled to withstand periods of relative deficiency of vitamin D which otherwise would produce rickets or osteomalacia. This compensatory mechanism is adequate to protect against relative degrees of deficiency of vitamin D; it is inadequate, as would be expected, when deficiency of vitamin D is extreme.

We are indebted to the Eli Lilly Company for supplying the parathormone used in this investigation.

BIBLIOGRAPHY

1. DEMOLE, V., and CHRIST, A.: Wirkung des D-Vitamins am Nebenschilddrüsenextirpierten Hund, *Arch. f. exper. Path. u. Pharmacol.*, 1929, cxlvi, 361-376.
2. ERDHEIM, J.: Tetania parathyreopriva, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1906, xvi, 632-744.
3. ERDHEIM, J.: Über Epithelkörperbefunde bei Osteomalacia, *Sitzungsb. d. Akad. d. Wissensch. Mathemat.-naturw. Kl., Abt. 3*, 1907, cxvi, 311-370.
4. ERDHEIM, J.: Über den Kalkgehalt des wachsenden Knochens und des Callus nach der Epithelkörperchenextirpation, *Frankf. Ztschr. f. Path.*, 1911, vii, 175-230.
5. ERDHEIM, J.: Rachitis und Epithelkörperchen, *Wien*, 1914, 321 pp.
6. HAMILTON, B., and SCHWARTZ, C.: Rickets and hyperparathyroidism, *Proc. Am. Soc. Clin. Invest., Jr. Clin. Invest.*, 1932, xi, 817.
7. HESS, A. F., and LEWIS, J. M.: Clinical experience with irradiated ergosterol, *Jr. Am. Med. Assoc.*, 1928, xci, 783-788.
8. HESS, A. F., WEINSTOCK, M., and RIVKIN, H.: Effect of thyroparathyroidectomy on the action of irradiated ergosterol, *Proc. Soc. Exper. Biol. and Med.*, 1929, xxvi, 555-556.
9. HESS, A. F., WEINSTOCK, M., and RIVKIN, H.: A further report on the effect of thyroparathyroidectomy on the action of irradiated ergosterol, *Proc. Soc. Exper. Biol. and Med.*, 1930, xxvii, 298-299.
10. HIGGINS, G. M., and SHEARD, C.: Effects of selective solar irradiation on the parathyroid glands of chicks, *Am. Jr. Physiol.*, 1928, lxxxv, 299-310.
11. HIGGINS, G. M., SHEARD, C., and WILDER, R. M.: The effect of ultra-violet irradiation on rachitic chickens, *Anat. Rec.* (In press.)
12. JOHNSON, J. L.: Experimental chronic hyperparathyroidism; effects of administration of irradiated ergosterol, *Am. Jr. Med. Sci.*, 1932, clxxxiii, 776-784.
13. KLEMPERER, P.: Parathyroid hyperplasia and bone destruction in generalized carcinoma-tosis, *Surg., Gynec. and Obst.*, 1923, xxxvi, 11-15.
14. KOZELKA, F. L.: Reproduction and lactation in the absence of the parathyroid glands and their probable function, *Proc. Jr. Biol. Chem.*, 1933, c, page lx.
15. KOZELKA, F. L., HART, E. B., and BOHSTEDT, G.: Growth, reproduction, and lactation in absence of parathyroid glands, *Jr. Biol. Chem.*, 1933, c, 715-729.
16. NONIDIZ, J. F., and GOODALE, H. D.: Histological studies on endocrines of chickens deprived of ultra-violet light; parathyroids, *Am. Jr. Anat.*, 1927, xxxviii, 319-347.
17. SEEDS, L., and REED, C. I.: Administration of viosterol in human parathyroid tetany. *Proc. Soc. Exper. Biol. and Med.*, 1931, xxviii, 379-380.

CHRONIC PERICARDIAL EFFUSION IN MYXEDEMA: REPORT OF CASE*

By E. B. FREEMAN, M.D., F.A.C.P., *Baltimore, Maryland*

THE cardiac disturbances associated with hyperthyroidism have long been recognized, as shown by the abundance of literature which has accumulated on the subject. Equally striking is the comparative dearth of publications dealing with the cardiac disturbances associated with hypothyroidism. In fact, nothing on this subject is to be found in the literature until 1918, when Zondek¹ described under the term "Myxedema Heart" certain cardiac signs and symptoms observed in some myxedematous patients, namely: enlargement of the heart, feeble heart action, slow heart beat, normal blood pressure, and low amplitude of the auricular P- and the final ventricular T-waves in the electrocardiogram. Since Zondek's original article was published, other articles dealing with the heart in myxedema have appeared in the literature at irregular intervals. The characteristic appearance of the heart as described by Zondek has been attributed to a number of conditions, namely: diffuse dilatation of the heart; edema of the heart and the tissues surrounding the heart; cardiovascular disturbances not dependent upon myxedema; and possibly to effusion into the pericardium. Since it has been proved that pleural and peritoneal effusions occur in some cases of myxedema, it seems logical to assume that a similar collection of fluid may likewise occur in the pericardium.

Fahr² believes that heart failure is a prominent feature in pronounced cases of myxedema. He claims that the shape of the heart in myxedema is very characteristic and differs very materially from that found in well known types of cardiac disease. He states that in defects of the mitral valve, there is bulging of the conus arteriosus and the pulmonary artery in the second and third interspaces, with displacement of the right auricular border to the right. In myxedema heart, this bulging does not occur. In lesions of the aortic valve and in hypertension, cardiac dilatation involves the left ventricle exclusively or, in the later stages, to a greater extent than the right. This again differs from myxedema heart in which all chambers dilate equally. Fahr further states that in a pericardial effusion of moderate degree, the heart shadow may resemble that seen in myxedema heart. In massive effusion, however, the base of the heart is much broader than in myxedema heart. He stresses the point brought out by Zondek, that when the myxedema heart is examined fluoroscopically, the heart borders move very sluggishly. This he attributes to marked dilatation; and he does not believe that any conclusion as to the strength of contraction can be drawn from observation of the heart borders.

Means, White and Krantz³ made an analysis of the cases of myxedema studied in the Thyroid Clinic of the Massachusetts General Hospital, cover-

*Presented to the Baltimore City Medical Society, March 3, 1933.

ing a period of 12 years—48 in all. They found one case only in which there was definite cardiac enlargement, which subsided under thyroid therapy. The initial enlargement in this case was not as pronounced as in Fahr's cases. From their study, they concluded that myxedema heart, in the sense of Zondek and Fahr, is far from common. They are not, however, willing to join those who feel that it does not exist. They further state that the evidence produced by Zondek and Fahr of marked cardiac dilatation which disappears quickly under thyroid medication, is incontrovertible; and their case, in a less striking way, is one in point. They believe the type of disability described by Zondek and Fahr must be functional in character, in that it responds so well to thyroid therapy. They have, however, no explanation as to why myxedema heart is not more frequently found in cases of myxedema.

Means,⁴ in a more recent article, suggests that the cardiac enlargement found in some cases of myxedema may possibly be due either to hypertrophy, pericardial effusion, edema or dilatation. "Because of the rapid shrinkage, hypertrophy is unlikely (unless of course, some independent cause for it, like hypertension, is present). By the same token, dilatation seems likely. At least, it is easy to believe that shrinkage could be due to the rapid improvement in tone under the action of thyroid. Pericardial effusion is possible, but the x-ray appearance is against it. Some edema of the heart muscle may play a part. It was noted at autopsy in our cases, and it is easy to conceive of its rapid disappearance under thyroid."

Lerman, Clark and Means,⁵ in a still more recent article, arrived at the following conclusions: "Myxedema heart in the sense of cardiac enlargement which undergoes shrinkage on thyroid medication is common. . . . The heart changes are to be regarded as a part of myxedema—not as a separate cardiac entity. . . . The change in the heart with thyroid treatment is probably due to increased muscle tonus and loss of interstitial edema. In an occasional case the loss of pericardial fluid may account for this change."

Willius and Haines⁶ made a careful study of 162 cases of high grade myxedema, with special reference to the cardiovascular system. As to age incidence, they found the disease was most frequent in the fourth, fifth, and sixth decades, in which 32, 52 and 38 cases, respectively, were recorded; there were 128 females and 34 males. In 148, or 91 per cent, there were no subjective symptoms or objective signs indicative of cardiovascular disease. Eleven cases, or 7 per cent, presented definite evidence of organic cardiovascular disease, which was only in one instance influenced by the disappearance of myxedematous symptoms under thyroid therapy. Their conclusions were as follows: "In 162 cases of high grade myxedema studied, none of heart failure and none of organic cardiovascular disease were found that could be justly attributed to the myxedema. There were numerous electrocardiographic abnormalities which disappeared under thyroid medi-

cation. The data presented do not justify the establishment of a cardiac syndrome characteristic of myxedema."

Ayman, Rosenblum and Falcon-Lesses⁷ analyzed 22 cases of myxedema heart previously reported in the literature, and report two additional cases that have come under their observation. They mention as probable causes of myxedema heart: cardiac dilatation secondary to a flabby heart muscle; myxedematous conditions of the heart itself or the tissue about the heart; and the existence of pericardial fluid.

Evans⁸ reports a case of myxedema with ascites and atony of the urinary bladder. He mentions six cases of ascites associated with myxedema previously reported in the literature. Five of these were reported by Fournier; in two of the five, there was also pleural effusion. The sixth was reported by Marsh. In this case three gallons of fluid were removed by abdominal paracentesis, following which the fluid gradually returned. It finally disappeared under thyroid therapy. In his summary he states: "A case is reported of well advanced myxedema presenting the unusual features of atony of the bladder, myxedema heart, and free fluid in the abdominal and pleural spaces. The fluid in the abdomen was found to have an unusually high protein content. It is believed that the atony of the bladder was a result of thyroid insufficiency and that the free fluid represented true myxedema fluid and not a manifestation of cardiac failure."

In a personal communication Christian⁹ states: "So far as I know, there are no observations in the literature in regard to pericardial effusion in myxedema. From time to time, people have expressed the idea that so-called myxedema heart was pericardial effusion and not an involvement of the myocardium, but I think no one has proved this. . . . The rapid decrease in the size of the heart following thyroid administration has also made this explanation of pericardial effusion probable. However, the only real proof will be the actual tapping of the pericardium with removal of the fluid. I have myself observed and proved by tapping, both peritoneal and pleural, accumulations of fluid in myxedema, and then have seen them disappear with thyroid extract. Consequently, I am entirely expectant of seeing the same thing happen with the pericardium."

Gordon,¹⁰ in a report on "Some Clinical Aspects of Hypothyroidism," calls attention to the occasional similarity of its clinical manifestations to those of pernicious anemia, chronic nephritis, migraine, and pericarditis with effusion. In his paper, he describes one case of myxedema with pericardial effusion occurring in a man of 68, whose complaints were shortness of breath and swelling of the face and lower extremities. On physical examination the cardiac dullness measured 24 centimeters laterally; the heart sounds were almost inaudible; roentgen-ray examination confirmed the presence of pericardial effusion. The basal metabolic rate was minus 22. On two occasions, the pericardium was tapped and 1500 c.c. of clear amber fluid were removed. Inoculation of a guinea pig with this fluid yielded no evidence of tuberculosis. On properly graduated doses of

thyroid extract the basal metabolic rate returned to normal, and the pericardial effusion disappeared.

In view of the fact that so few cases of effusion into the serous cavities of the body in myxedema have been reported and since, as far as I am able to determine, in only one of these did the effusion occur in the pericardial sac, I herewith submit the following report:

CASE HISTORY

A. W. H., male, aged 39, referred by Dr. George W. Murgatroyd, entered the Maryland General Hospital on March 23, 1931. His family history was unimportant. His past history was negative with the exception of an illness at the age of six, which was possibly rheumatic fever. His present illness began in 1925, when he was 33

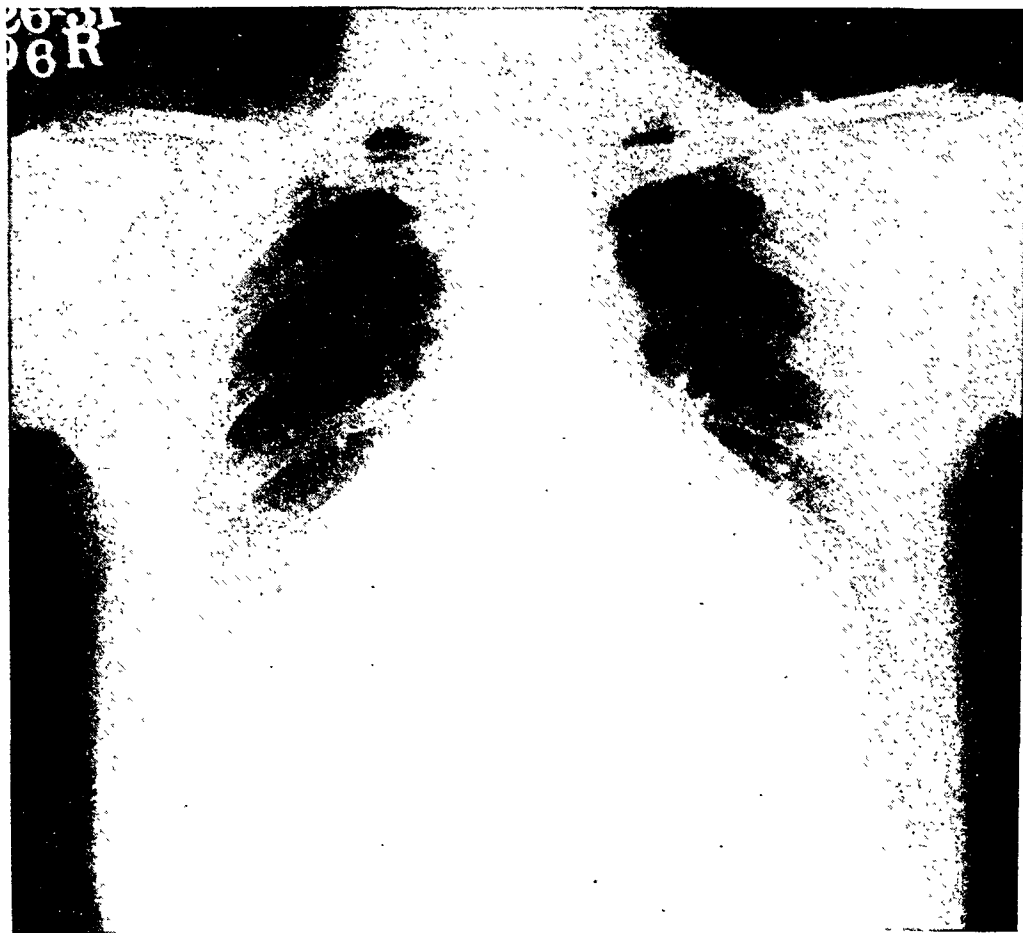


FIG. 1. Chest film on admission before pericardium was tapped.

years of age, with a feeling of exhaustion. He continued to work until March 1, 1927. One week later, he entered St. Agnes' Hospital. An abstract of the St. Agnes' Hospital records is herewith presented:

Chief Complaint: Marked weakness associated with cough and shortness of breath. Physical examination: pale, anemic looking young man. Skin very dry and

scaly; hair thick and dry; eyelids edematous; thyroid not palpable. Cardiac dullness increased to the left to the mid-axillary line; and likewise definitely increased to the right, with obliteration of the cardio-hepatic angle. The increase in the area of cardiac dullness found on physical examination was confirmed by roentgen-ray study. No murmurs were heard and there was no arrhythmia. The blood pressure was 110 systolic and 70 diastolic. The lungs showed moderate dullness at both bases posteriorly. The abdomen was soft, and the liver enlarged; its lower border was three fingers' breadth below the costal margin, somewhat firmer than normal, the surface smooth and regular. There was slight edema of the extremities. The reflexes were normal.



FIG. 2. Chest film taken immediately after withdrawing 450 c.c. of fluid from pericardium.

The records show the following laboratory studies: Blood Wassermann negative. Hemoglobin 70 per cent; erythrocytes 4,500,000; leukocytes 10,300; normal differential count. Van den Bergh test: direct and indirect negative. Icterus index 5. Stomach analysis (test meal): free hydrochloric acid 10 degrees; total acidity 19. Urine: specific gravity 1.020; tests for sugar and albumin negative; microscopic examination negative. Renal function test (intravenous phenolsulphonphthalein): first half hour 15 per cent; second half hour 8 per cent; total 23 per cent.

A diagnosis of chronic pericarditis with effusion was made. The pericardium was tapped and 1400 c.c. of a clear, straw colored fluid were removed. The specific gravity was 1.019. The patient remained in St. Agnes' Hospital for four weeks and was discharged very much improved. He returned to his trade, electrotyping, and worked for three months in the early summer of 1927. During this time there was

a gradual return of symptoms, and he was again compelled to give up his position. From the time he gave up his position in August 1927 until he entered the Maryland General Hospital in March 1931 (nearly four years), he remained a semi-invalid and unable to work. When he entered the Maryland General Hospital, he presented a typical picture of myxedema. His chief complaints were shortness of breath, pronounced weakness, swelling of the extremities, and great sensitiveness to cold. He was mentally very sluggish and responded to questions slowly. The least effort seemed completely to exhaust him. He was unable to lie down in comfort on account of shortness of breath. There was marked puffiness of the eyelids and face. There



FIG. 3. X-ray film taken immediately after removal of 800 c.c. of fluid from pericardium, 14 days following first tapping.

was slight pitting edema of the lower extremities. His skin was very dry; it was especially scaly on the arms and legs, and apparently somewhat thickened everywhere. The hair was extremely dry, very coarse and thick. There was no loss of hair on any portion of the body, except on the legs below the knees. His tongue was coated and very dry. The area of cardiac dullness was markedly increased, with a transverse measurement of 24 centimeters; the cardio-hepatic angle was obliterated. The physical signs of enormous increase in the area of cardiac dullness were confirmed by fluoroscopy and roentgen-ray films. In addition to confirming these physical findings, the fluoroscopic study also showed complete absence of pulsation in the cardiac shadow. The apex beat was not visible; it was barely possible to hear the heart sounds. The pulse rate was 70 per minute and regular. The blood pressure was 120 systolic and 70 diastolic. No sclerosis of the peripheral vessels was apparent. The

lungs showed a few moist râles at both bases posteriorly. There was no shifting abdominal dullness. The liver was enlarged; its lower border was three fingers' breadth below the costal margin, somewhat firmer than normal, and not sensitive to pressure. There was slight edema of the extremities. The deep reflexes gave responses within normal limits.

Special Studies: Blood Wassermann negative. Hemoglobin 75 per cent; erythrocytes 3,750,000; leukocytes 7,100; normal differential count. Blood urea 32.4 milli-

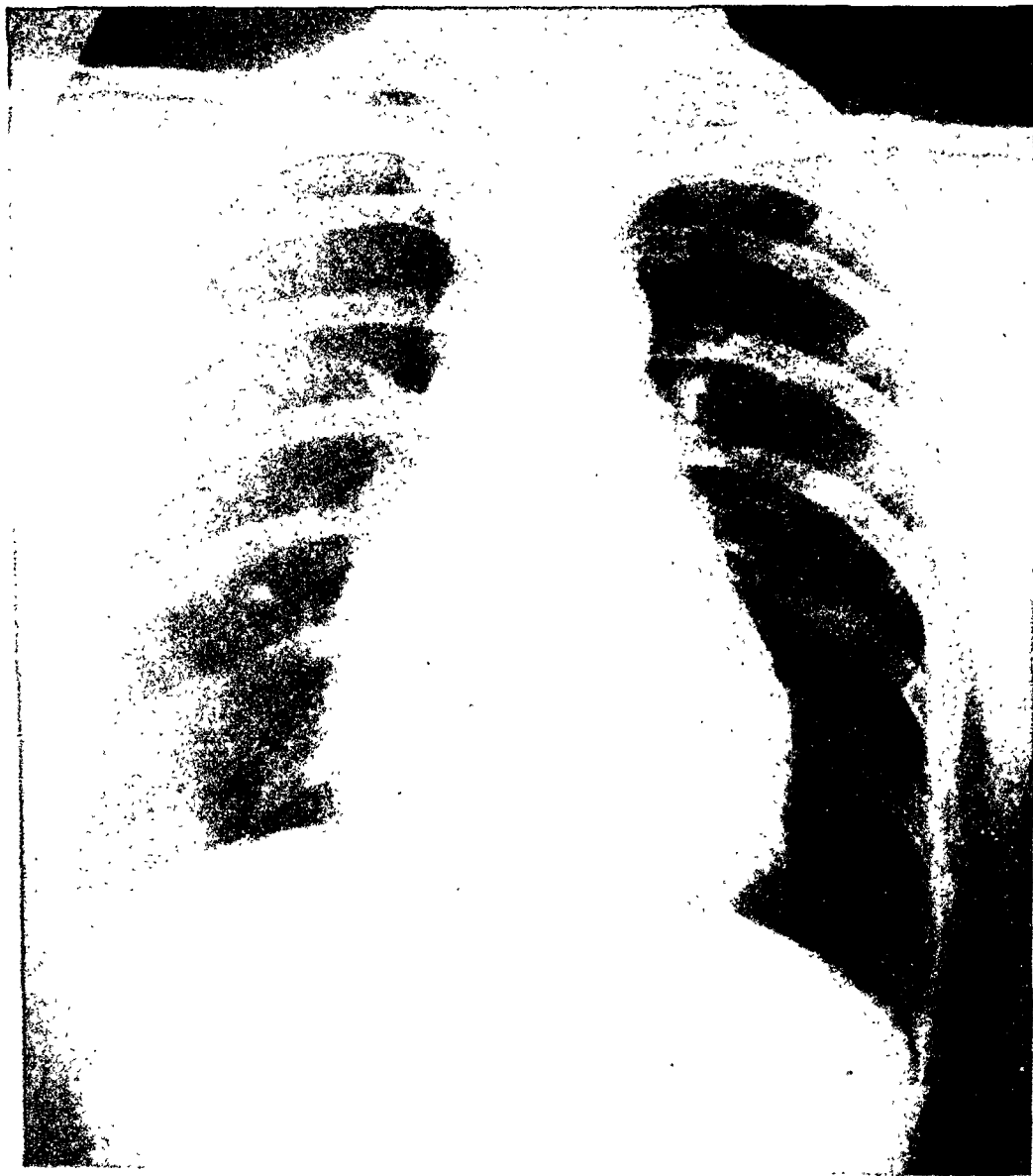


FIG. 4. X-ray film, three months after patient began taking thyroid extract.

grams per 100 c.c. blood. Stomach analysis (test meal): free hydrochloric acid 8 degrees; total acidity 22 degrees. Urine: specific gravity 1.010; albumin, trace; sugar negative; microscopic examination negative. The electrocardiogram showed the absence of P waves and low amplitude of the QRS complexes. The basal metabolic rate was -35. A diagnosis of myxedema with chronic pericardial effusion was made. The pericardium was tapped and 425 c.c. of clear, straw colored fluid removed. Two weeks later the pericardium was again tapped, and an additional 800

c.c. of fluid removed. Even though 800 c.c. of fluid were removed, a large quantity still remained, as evidenced by roentgen-ray films taken immediately after the pericardium had been tapped. The fluid contained no blood and formed no clots; its specific gravity was 1.022. The Rivalta test was positive; protein 45 grams per liter. Smears: polynuclear cells 50 per cent, lymphocytes 12 per cent, endothelial cells 38 per cent. No organisms were found. Stained smears showed no tubercle bacilli; culture on blood agar remained sterile; guinea pig inoculation proved negative for tuberculosis.

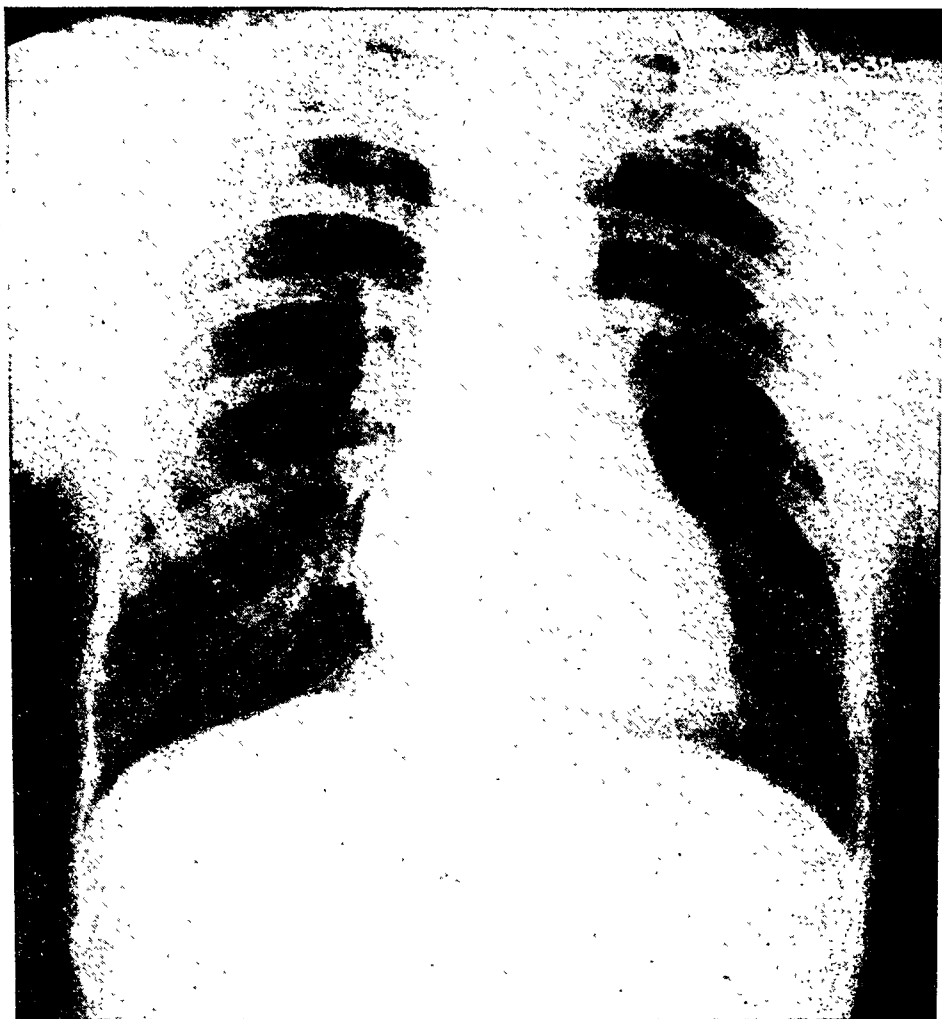


FIG. 5. X-ray film, 17 months after beginning of thyroid extract.

It is interesting to note the striking resemblance that exists between the clinical history, physical examination and the laboratory studies made in St. Agnes' Hospital and those made in the Maryland General Hospital four years later. When this is borne in mind, I think one is justified in drawing the following conclusions: (1) that the large pericardial effusion found in St. Agnes' Hospital was not due, as thought, to chronic pericarditis but to myxedema; (2) that the patient had been suffering from myxedema from the onset of his symptoms, which were first noticed six years before thyroid therapy was instituted.

The initial dose of thyroid extract was small, $\frac{1}{4}$ grain three times a day. The dose was gradually increased until at the end of three months, the patient was getting $\frac{3}{4}$ grain three times a day. This amount of thyroid brought the basal metabolic rate up from a minus 45 to a minus 10. With this rise in metabolic rate, the pericardial effusion entirely disappeared as shown by physical examination and roentgen-ray study. There was marked improvement in the patient's general condition. His mental condition returned to normal, and he became interested in life for the first time in

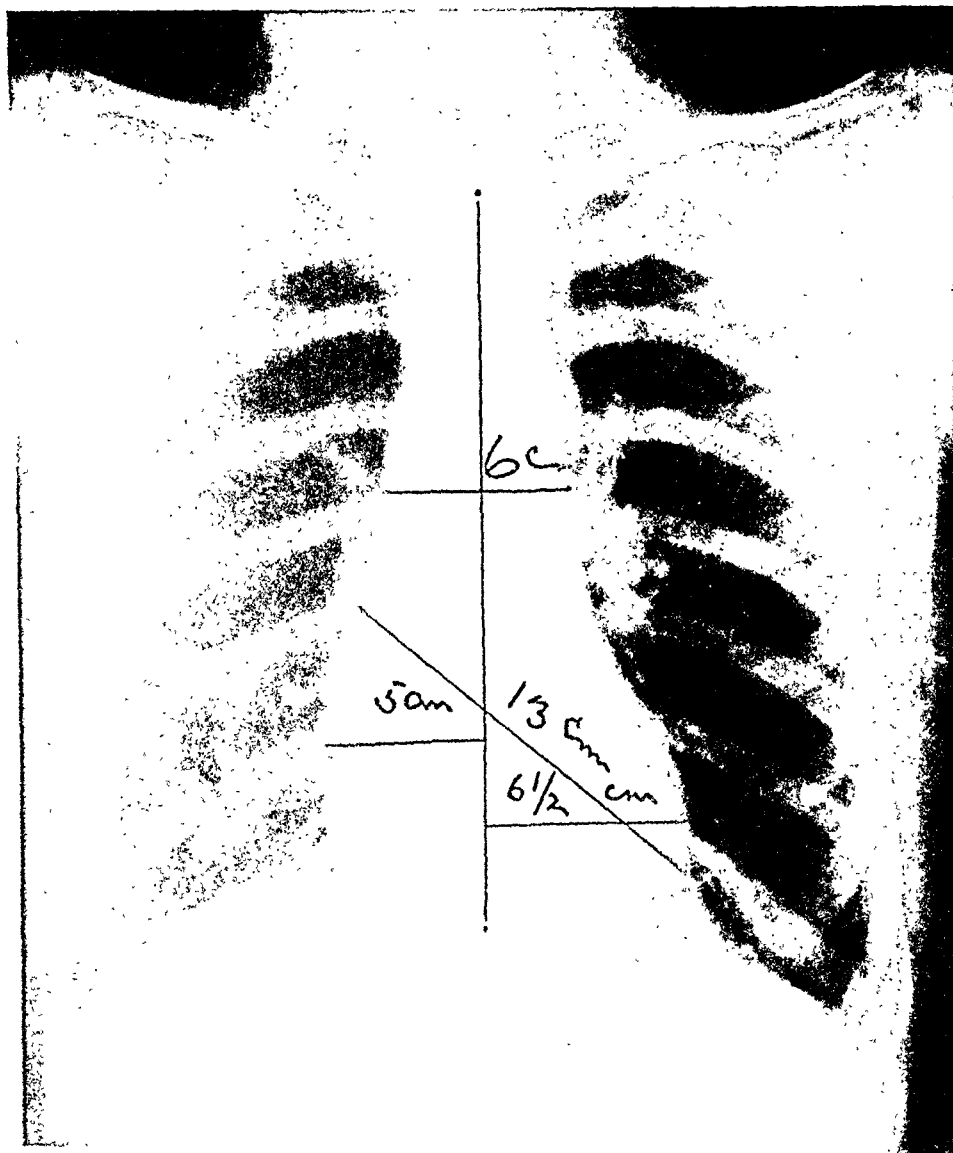


FIG. 6. Teleroentgenogram, 26 months after beginning thyroid therapy.

more than four years. The skin was moist. The edema of the face and extremities entirely disappeared and the subcutaneous thickening noticed over the entire body likewise disappeared. The electrocardiographic tracing returned to normal. The muscular weakness was very much improved. There was no attempt made to give sufficient amount of thyroid to bring the basal metabolic rate up to an absolute normal, but it seemed better judgment in this particular case to keep the metabolic rate around minus 10, this has been done. Basal metabolic studies have been made every six months. The amount of thyroid extract required to keep the metabolic rate around minus 10 has remained constant,— $2\frac{1}{2}$ grains per day for the past 18 months.

In addition to the basal metabolic determinations made at regular intervals, there have been frequent roentgen-ray studies of the heart. The heart has remained normal in size. Since the fluid disappeared from the pericardium there has been no evidence of its return. Only once since thyroid treatment was begun has it been discontinued. This was done at the suggestion of Dr. William F. Rienhoff in an effort to determine whether or not there was any change in the calcium content of the blood in chronic pericardial effusion in myxedema. The first calcium determination was made while the patient was still taking thyroid extract; this showed 10.5 milligrams of calcium per 100 c.c. blood. Thyroid therapy was discontinued for 16 days, when a second calcium determination was made; this showed 10 milligrams per 100 c.c. blood. These two determinations approximate each other so closely that it seems apparent that the stopping of the thyroid did not influence the calcium content of the blood. There was, however, a drop of 22 per cent in the basal metabolic rate in the 16 day period during which the thyroid therapy was discontinued. It is now two and a half years since thyroid therapy was instituted. Throughout this time thyroid extract has been given continuously, except for the short intermission while the blood calcium determinations were being made. No other medication has been given. While the patient's physical condition has not improved sufficiently to enable him to return to his occupation of electrotyping, he has been able, however, to do less strenuous work and has been holding a responsible office position for the past four months. He looks and feels quite well.

SUMMARY

A case of chronic pericardial effusion occurring in myxedema is presented. The pericardial effusion was rapidly absorbed when sufficient thyroid was given to bring the metabolic rate up to the accepted low normal. It seems apparent therefore, that chronic pericardial effusion does occur in some cases of myxedema, although the etiological relationship of the myxedema to the pericardial effusion is not clearly understood.

BIBLIOGRAPHY

1. ZONDEK, H.: *Das Myxödemherz*, München. med. Wchnschr., 1918, lxxv, 1180-1182; 1919, lxxvi, 681-683.
2. FAHR, G.: Myxedema heart, *Jr. Am. Med. Assoc.*, 1925, lxxxiv, 345-349.
3. MEANS, J. H., WHITE, P. D., and KRANTZ, C. I.: Heart in myxedema, with special reference to dilatation and angina pectoris, *Boston Med. and Surg. Jr.*, 1926, cxcv, 455-460.
4. MEANS, J. H.: Hypothyroid heart disease, *New England Jr. Med.*, 1933, x, 541-543.
5. LERMAN, J., CLARK, R. J., and MEANS, J. H.: The heart in myxedema, *ANN. INT. MED.*, 1933, vi, 1251-1271.
6. WILLIUS, F. A., and HAINES, S. F.: Status of heart in myxedema, *Am. Heart Jr.*, 1925, i, 67-72.
7. AYMAN, D., ROSENBLUM, H., and FALCON-LESSES, M.: "Myxedema heart" without evidence of cardiac insufficiency, report of two cases, *Jr. Am. Med. Assoc.*, 1932, xcvi, 1721-1725.
8. EVANS, W.: Case of myxedema with ascites and atony of urinary bladder, *Endocrinology*, 1932, xvi, 409-416.
9. CHRISTIAN, H. A.: Personal communication.
10. GORDON, A. H.: Some clinical aspects of hypothyroidism, *Canadian Med. Assoc. Jr.*, 1929, xx, 7-10.

THE EFFECT OF CALCIUM ON THE STORAGE OF COLLOID IN THE THYROID GLAND*

By JACOB KLEIN, M.D., *Chicago, Illinois*

For some time iodine has been emphasized as the most important factor in thyroid function. Iodine, however, is only one factor. Calcium is another element necessary to proper thyroid function. Various aspects of the problem have been discussed by Berry,¹ Hellwig,² Kottman,³ Abelin,⁴ and Juanita Thompson.⁵ As the latter has stated, both calcium and iodine exert important influences on the thyroid, the normal function of which seems to depend on a proper relation between these two elements. Calcium in limestone areas has been stressed as an important factor in the causation of goiter, through a water supply rich in this element. More recently Hellwig has demonstrated that excess of calcium in the presence of iodine deficiency causes hyperplastic changes in the thyroid. The results of his investigations suggest again that normal thyroid function may depend on the conjoint action of calcium and iodine. The purpose of my study is to determine what influence calcium exerts in the storage of colloid in the thyroid; particularly in the presence of thyroglobulin as well as of an excess of iodine in the water supply. The investigation was begun as a result of an interesting clinical experience in which the administration of calcium exerted a definite curative effect in acute hyperthyroidism.⁶ This raised the question: What effect has calcium on the function and structure of the thyroid gland which gives it therapeutic properties in clinical hyperthyroidism?

EXPERIMENTS

Thirty-six young white rats, 250 to 300 grams in average weight, were separated into six groups, which were kept separate in clean wire cages and were all fed a liberal general diet. Group 1 received distilled water for drinking and daily injections of 0.5 c.c. of a 2 per cent hog thyroglobulin. Group 2 was given 5 per cent calcium lactate water for drinking, and daily injections of 0.5 c.c. of a 2 per cent solution of thyroglobulin. Group 3 received distilled water for drinking, daily injections of thyroglobulin, and a daily subcutaneous injection of 1 c.c. of a 10 per cent solution of calcium gluconate. Series 1 to 3 were started on April 27, 1932 and were terminated by chloroforming on May 16, 1933. The thyroids were immediately dissected out, measured, and fixed in 10 per cent formalin. Group 4 was given 1 per cent potassium iodide in distilled water for drinking and no calcium. Group 5 received 1 per cent potassium iodide in distilled water for drinking, and daily injections of 1 c.c. of a 10 per cent solution of calcium gluconate. Groups 4 and 5 were begun on May 20, 1933 and chloroformed on June 20,

* Received for publication December 1, 1933. From the John McCormick Institute for Infectious Diseases.

1933. In group 4, two rats died of intercurrent infection. These were rejected. A series of six rats on the general laboratory diet and tap water served as controls. The thyroid tissues were imbedded in celloidin and sections 10 to 15 microns thick were stained with hematoxylin and eosin. Thick sections were chosen because they give a better concept of the shape and size of the follicles. In order to render the results as objective as possible, measurements of the follicles were made with an ocular micrometer. In each animal the diameters of 25 of the largest follicles were measured in scattered sections of the series and the average follicular diameter computed. As a check on the accuracy of the measurements, 100 additional follicles were counted in scattered sections of each rat series and the results tabulated. (See tables 1 and 2.) Thus in each series 250 follicles were measured. Since peripheral follicles are often larger than internal ones, half of the measurements were taken in the center of a section. In this manner a certain estimate could be obtained as to the average size of the thyroid follicle which was used as an index of colloid storage.

RESULTS

The results of the gross thyroid measurements and follicular index are recorded in tables 1 and 2. The normal average follicular diameter was 214 microns. This is not presented as an absolute value: the variability of the structure of the thyroid gland under diverse conditions is well known. However, under the given conditions the index may serve as a measure for comparison. In the normal resting glands, the colloid was thin, and stained faintly with eosin. In the other groups the colloid seemed dense and was markedly eosinophilic. The rats receiving thyroglobulin and no calcium showed a slight increase of colloid storage as compared with the normal; 228 microns compared to 214 microns (6 per cent). The group receiving an excess of calcium lactate in the drinking water presented the greatest storage of colloid, 49 per cent above normal. The calcium gluconate group also showed a definite increase in colloid storage, 33 per cent above normal, as compared with a 6 per cent increase with thyroglobulin alone. This appears to demonstrate that calcium increases the storage of colloid in the presence of an experimental excess of thyroglobulin. This fact may explain the therapeutic action of calcium in clinical hyperthyroidism. The storage of colloid in the presence of excessive amounts of iodine is illustrated by series 4 and 5. With no calcium, 1 per cent potassium iodide caused an apparent 10 per cent increase of colloid storage as compared to the normal. However, with the administration of calcium gluconate in the presence of an excess of iodine this increase reached 38 per cent. In group 3, rat 5 had a rather low follicular index (141 microns) and epithelial hyperplasia. This was associated with a suppuration in the trachea. The same applies to rat 2 in group 4, and rat 4 in group 5. Nevertheless the rats which received calcium showed greater colloid storage even in the presence of

TABLE I

Rat Series	Group 1 Distilled H ₂ O Thyroglobulin		Group 2 Calcium Lactate Thyroglobulin		Group 3 Calcium Gluconate Thyroglobulin		Group 4 1% KI Water No Calcium		Group 5 1% KI Water Calcium Gluconate		Group 6 Normal Diet Control Series	
	Diam- eter of Follicles, Microns	Size of Thyroid, Milli- meters	Diam- eter of Follicles, Microns	Size of Thyroid, Milli- meters	Diam- eter of Follicles, Microns	Size of Thyroid, Milli- meters	Diam- eter of Follicles, Microns	Size of Thyroid, Milli- meters	Diam- eter of Follicles, Microns	Size of Thyroid, Milli- meters	Diam- eter of Follicles, Microns	Size of Thyroid, Milli- meters
1	200	R.5×2×1 L.5×2×1	274	R.5×2×1 L.5×2×1	340	R.5×2×1 L.5×2×1	333	R.6×3×2 L.6×3×2	311	R.5×2×1 L.5×2×1	174	R.6×3×1 L.6×2.5×1
2	251	R.6×2×1 L.6×2×1	333	R.5×2×1 L.5×2×1	290	R.6×2×2 L.6×2×2	189*	R.7×3×1 L.7×3×1	332	R.6×2×1 L.6×2×1	242	R.5×2×1 L.5×2×1
3	250	R.5×2×1 L.5×2.5×1	411	R.5×2×1 L.5×2×1	343	R.6×2×1.5 L.6×2×2	254	R.6×2.5×1 L.6×2.5×1	349	R.5×2.5×1 L.5×2.5×1	244	R.6×2×1.5 L.6×2×1.5
4	248	R.4×2×1 L.4×2×1	393	R.6×2×1 L.6×2×1	298	R.6×2×1 L.6×2×1	192	R.8×3×2 L.8×3×2	208*	R.5×2×1 L.5×2.5×1	224	R.5×2×2 L.5×2×2
5	238	R.5×2×1 L.5×2×1	292	R.5×2×2 L.5×2×2	141*	R.6×2×1 L.6×2×1	Died Rejected	R.7×3×1 L.7×3×1	308	R.6×2×1 L.6×2×1	213	R.6×2×2 L.6×2×2
6	173	R.5×2×1 L.5×2×1	276	R.5×2×1 L.5×2×1	379	R.6×2×1 L.6×2×1	Died Rejected	R.6×2×1 L.6×2×1	329	R.6×2×1 L.6×2×1	201	R.6×2×1 L.6×2×1
Average Diameter 226			329		297		242		306		216	

* Respiratory Infection; Suppuration in Trachea.

TABLE II
(100 Follicles in Each Series)

<i>Group 1</i> Distilled H ₂ O- Thyroglobulin	<i>Group 2</i> Calcium Lac- tate-Thyro- globulin	<i>Group 3</i> Calcium Glu- conate-Thyro- globulin	<i>Group 4</i> 1% KI Water No Calcium	<i>Group 5</i> 1% KI Water Calcium Gluconate	<i>Group 6</i> Normal Diet Control-Series
Diameter of Follicles, Microns	Diameter of Follicles, Microns	Diameter of Follicles, Microns	Diameter of Follicles, Microns	Diameter of Follicles, Microns	Diameter of Follicles, Microns
230	309	274	230	287	213
Average Measurement for 250 Follicles					
218	319	285	236	296	214

infection. Gross measurements indicated abnormal size of follicles (colloid goiter) in rats 2, 4, and 5 in the group receiving 1 per cent potassium iodide water and no calcium. All the other animals presented practically normal measurements of the total thyroid gland (5 by 2 by 1 to 6 by 2.5 by 1 mm.). The gross appearance of the cut surface varied. The gland might appear pink with much colloid, or hyperemic and seemingly poor in colloid.

SUMMARY

1. Calcium either by mouth or hypodermically increases the amount of colloid in the thyroid gland in the rat in the presence of excess of thyroglobulin and iodine.

2. Intercurrent respiratory infection may cause a decrease of colloid storage and of hyperplasia. Even in these animals calcium increased the storage of colloid.

3. The therapeutic action of calcium in hyperthyroidism may be due to this property of increasing colloid storage in the presence of an excess of thyroglobulin.

BIBLIOGRAPHY

1. BERRY, J.: Goiter; its pathology, diagnosis and surgical treatment, Brit. Med. Jr., 1891, i, 1269-1273.
2. HELLWIG, C. A.: Iodine deficiency and goiter; influence of diet poor in iodine on thyroid gland in white rats, Arch. Path., 1931, xi, 709-722.
3. KOTTMAN, A.: Kolloidchemische Untersuchungen über schilddrüsen Probleme, Schweiz. med. Wchnschr., 1920, 1, 644.
4. ABELIN, I.: Schilddrüse und Mineralstoffwechsel. Einfluss des Dinatriumphosphats und der Calciumsalze auf die Wirkung der Schilddrüsen-substanzen, Biochem. Ztschr., 1928, cxcix, 72-106.
5. THOMPSON, J.: Influence of intake of calcium on thyroid gland of albino rat, Arch. Path., 1933, xvi, 211-225.
6. KLEIN, J.: The calcium treatment of hyperthyroidism, Med. Jr. and Rec., 1933, cxxxviii, 427-428.

NOMENCLATURE OF THE DISORDERS OF INSULIN SECRETION: DIABETES MELLITUS, HYPERINSULINISM AND DYSINSULINISM *

AN ANALYTICAL REVIEW OF DATA RELEVANT TO THE CLASSIFICATION AND TERMINOLOGY OF THE SECRETORY DISORDERS OF THE ISLANDS OF LANGERHANS OF THE PANCREAS

By SEALE HARRIS, M.D., F.A.C.P., *Birmingham, Alabama*

THE classification and nomenclature of the secretory disorders of the islands of Langerhans of the pancreas is of importance, as it is in all diseases. According to the recently compiled book, "A Standard Classified Nomenclature of Disease,"¹ which has been adopted by the leading hospitals in America, the ideal name for a disease should identify it with the organ involved (topographic), and with the pathologic and physiologic changes that occur in the glands, or other tissues, which cause the phenomena observed in the condition (etiologic). In the classification and nomenclature of the secretory disorders of the pituitary, thyroid and adrenal glands, the topographic and etiologic factors have been considered; thus it seems logical that the same method of nomenclature should be adopted in the terminology of the disorders of the internal secretion of the pancreas.

Rowe² in his recent book on "The Differential Diagnosis of Endocrine Disorders," discussing the terminology of the secretory disorders of the endocrine gland, says:

The term hypofunction is applied to that condition in which the clinical and laboratory findings indicate a lowered functional level—the extreme picture of which may be produced by complete ablation of the gland, in other words, a state of demonstrable diminution or lack of internal secretory activity.

Hyperfunction is used to indicate a condition in which all measurable abnormal function levels are of opposite sign to those pronounced by ablation.

Dysfunction states are those in which evidences of hyper- and hypo-activity are simultaneously observed. Such conditions arise, for example, when endocrine organs initially hyperactive are undergoing a functional evolution to an ultimate hypo-active state. Years ago Cushing called attention to such involutions in acromegaly, and the writer and his associates have frequently observed analogous conditions in thyroid disease.

In the nomenclature of the disorders of thyroid secretion, the following terms are in general use: hyperthyroidism, synonymous with toxic goiter, exophthalmic goiter, and Graves' disease; dysthyroidism, i.e., imperfect thyroid function; and hypothyroidism, synonymous with myxedema and cretinism. The secretory disturbances of the pituitary glands, described by Cushing and others, are called hyperpituitarism, dyspituitarism, and hypopituitarism. Likewise, hyperadrenalism, dysadrenia and hypoadrenalism

* Received for publication December 28, 1933.

are accepted terms for describing the syndromes resulting from the excessive, irregular, or deficient secretion of adrenin (epinephrin).

The discovery of insulin by Banting,³ and the observation that an excessive dose of insulin produces hypoglycemia with definite symptoms (Banting, Campbell and Fletcher,⁴ Noble and MacLeod,⁵) made it certain that some one would recognize cases resulting from the spontaneous excessive secretion of the hormone of the pancreas, which Schaffer⁶ had previously called insulin. In 1923, when nondiabetics were observed to have symptoms identical with those of an insulin reaction and found to have abnormally low blood sugars during the attacks, the question of the nomenclature of the disorders of the islands of Langerhans was considered.^{7a} It was logical to regard them as analogous to the secretory disorders of other organs of internal secretion, i.e., thyroid, pituitary, and adrenals, all of which had been recognized and named, using in their terminology, the prefix *hyper* when there was excessive secretion, *hypo* when there was deficient secretion, and *dys* when the secretion was irregular; and the suffix *ism* was used to refer to the state, or action, of the organ involved. It, therefore, would seem that the disorders resulting from the excessive, uncontrolled, or deficient internal secretion of the islet cells of the pancreas should be called respectively hyperinsulinism, dysinsulinism, and hypoinsulinism, the latter to be synonymous with, but never to supplant, the long accepted term diabetes mellitus.

Hypoinsulinism Synonymous with Diabetes Mellitus. If diabetes mellitus, a disease due to a deficiency of insulin, had been discovered since the scientific nomenclature of disease has been adopted it would be called hypoinsulinism; but the ancient Greeks, observing polyuria, called the disease associated with it diabetes, meaning a syphon, or a fountain; and when, according to tradition, bees were seen swarming around the urine of patients from whom urine flowed like water spouting from the syphon of a fountain, the term mellitus, meaning honey, was added. Thus the term diabetes mellitus has been used since the dawn of medical history to describe the disease entity characterized by hyperglycemia, polyuria, glycosuria, and a tendency to ketosis.

Greek medical nomenclature would not be regarded as altogether scientific in the twentieth century, but the names they gave many diseases are so expressive and impressive that they have lived through the centuries; and no doubt the term diabetes mellitus will endure until the end of time. Certainly the good old name diabetes mellitus, though not as scientific as hypoinsulinism, has merit, and with sanction of long usage, it will and should be continued to be used.

Until more of practical value has been proved regarding the independent action of the pituitary, thyroid and adrenal hormones in carbohydrate metabolism, it would seem that Allen, Joslin, Banting, Opie, Cecil, Warren and others, who are regarded as authorities on diabetes, are correct in their conclusion that diabetes mellitus is essentially due to the deficient secretion

of insulin. Therefore, the term hypoinsulinism may be used correctly, except perhaps in rare cases, as being synonymous with diabetes mellitus. Granting that extra-insular influences, as the excessive secretion of the antagonistic hormones by the hypophysis, thyroid and adrenals, were primarily responsible for decreased insulin production, or availability, in diabetes the expression hypoinsulinism would be just as appropriate as if there were actual lesions of the pancreas.

Hyperglycemia. Hyperglycemia, regardless of its etiology, is not a disease entity and should be classified as a condition, and not a disease, of the blood. Hyperglycemia cannot be considered as being synonymous with diabetes mellitus, though it usually is a manifestation of the disease.

Hyperglycemia occurs frequently in nondiabetics. In blood sugar studies (Folin-Wu method) up to October 1, 1933, on 3076 patients, most of them routine fasting blood sugars on patients sent to us for the diagnosis and treatment of gastrointestinal and nutritional disorders, 777 were found to have hyperglycemia. Of these, according to Joslin's criteria,^{9a} 535 had true diabetes mellitus leaving 242 of 2541 nondiabetics, or 9.5 per cent, who had fasting blood sugars of more than 0.120 per cent. Of these 242 hyperglycemics, in 187 the fasting blood sugars were between 0.121 and 0.140 per cent. In 36 who did not have glycosuria the blood sugars were between 0.141 and 0.160 per cent, while 19 nonglycosurics had blood sugars above 0.160 per cent. According to Priscilla White,⁸ associated with Joslin, all of the 19 with postprandial blood sugar rise above 0.160 per cent should be classified as true diabetics. This would bring our series of cases of diabetes to 554 up to October 1, 1933.

There no doubt is a higher incidence of hyperglycemia in our series of cases studied than would be found in general practice, or in a general hospital, because many of the patients on whom fasting blood sugars were made were referred for suspected diabetes; but this observation shows that hyperglycemia without diabetes occurs frequently. Certainly a patient cannot be assumed to have diabetes because he has hyperglycemia of a moderate degree. There are many diseases besides diabetes in which hyperglycemia occurs.

No one would think of reporting a case of hyperglycemia, unless the term were used as a functional diagnosis, or as a qualifying term added to the name of the disease of the pancreas or other organ, which was the primary cause of the high blood sugar; yet many clinicians have reported cases of "hypoglycemia," a condition which usually results from the opposite secretory disorder of the pancreas (hyperinsulinism), and which is no more a disease entity than hyperglycemia.^{7b}

Glycosuria. Glycosuria, like hyperglycemia, is usually a manifestation of diabetes, and is not a disease. Glycosuria, therefore, cannot be regarded as being synonymous with diabetes.

Joslin^{9a} is safe and conservative in his opinion that the glycosuric pa-

tient should be considered as a real or potential diabetic until proved otherwise. He said:

Glycosuria usually is dependent upon disease of the pancreas, particularly of the islands of Langerhans. My rule in the treatment of diabetes is to consider any patient who has sugar in the urine demonstrable by any of the common tests to have diabetes mellitus and to treat him as a diabetic until the contrary is proved. This procedure is safer for the patient, than to make use of the term glycosuria which begets indifference and may lead to disaster. It is convenient to classify patients with glycosuria, or with a history of glycosuria into four groups: true diabetics, potential diabetics, renal glycosurics, and unclassified diabetics. Under true diabetics are placed patients whose blood sugars on an unrestricted diet are 0.14 per cent or more fasting, or 0.17 per cent or more after a meal with simultaneous glycosuria which is plainly related to diet.

Joslin,^{9b} however, found in a study of 6000 glycosuric patients that only 5086, 85 per cent, had true diabetes, leaving 15 per cent of nondiabetic glycosurics.

In a recent study of our records up to October 1, 1933 of routine night and morning examinations of the urine of 6641 patients, largely adults usually referred by physicians for gastrointestinal and nutritional disorders, 818 had glycosuria. Applying Joslin's criteria^{9a} for establishing a diagnosis of true diabetes, i.e., the simultaneous presence of sugar in the urine, and fasting blood sugar of 0.14 per cent or more, or 0.17 per cent or more after a meal, 535 (66.6 per cent) were found to have diabetes, leaving 285 (33.4 per cent) of nondiabetics with glycosuria. Perhaps the reason why a larger percentage of glycosurics in our series were classed as nondiabetics than Joslin found in his larger series was because less than 10 per cent of our patients were diabetics, and no doubt a larger proportion of the patients referred to Joslin are sent because of actual or suspected diabetes.

Many of our nondiabetics in whom sugar was found in the routine examination of urine were studied for only one or two days, so it is probable that many of them would have been found to have true diabetes if time had been given for glucose tolerance tests. From these observations the conclusion must be drawn that glycosuria without diabetes is relatively frequent in many conditions. Glycosuria, therefore, has no place in the terminology of the disorders of insulin secretion, except as a qualifying functional diagnosis of many diseases.

Of the 181 nondiabetics in our series with moderate hyperglycemia, i.e., fasting blood sugar between 0.121 and 0.140 per cent, 29 had glycosuria. Most of this group, particularly those with both moderate hyperglycemia and glycosuria, were considered as potential diabetics. No doubt many of them would have been found to be true diabetics had the opportunity been given to make glucose tolerance tests upon them.

It is interesting to note that, up to October 1, 1933, of 218 nondiabetic patients with hypoglycemia, i.e., with fasting blood sugars below 0.080 per cent, 42 (19 per cent) had sugar in their urine. In 86 of these, in which there seems to be no doubt of the diagnosis of hyperinsulinism, 22 (26 per

cent) had glycosuria. Several of these were sent in diagnosed from the glycosuria, without blood sugar studies, as diabetes. Of 58 hypoglycemics, considered as borderline cases of hyperinsulinism, 11 (19 per cent) had glycosuria. Of 74 hypoglycemics without symptoms of hyperinsulinism, 9 (12.2 per cent) had glycosuria.

As a check, the incidence of glycosuria in conditions in which there was no evidence of disturbed insulin secretion was studied. In 576 patients diagnosed as having gastric and duodenal ulcers, in routine examination of night and morning specimens of urine, 44, a percentage of 7.8, were found with glycosuria. In 978 diagnosed as psycho-neurasthenia, usually with symptoms due to gastrointestinal neuroses, only 58, or 5.9 per cent, had sugar in their urine.

The conclusion must be drawn from these studies that glycosuria is found in many diseases besides diabetes; and that since glycosuria was found in 26 per cent of patients with hypoglycemia and symptoms of hyperinsulinism, the low renal threshold may be due to disturbed insular function.

HYPERINSULINISM

The terminology of the recently recognized disorders resulting from the assumed excessive secretion of insulin, or deficiency of anti-insulin substance, has been discussed by a number of clinicians who have reported cases of patients suffering from hypoglycemic symptoms. In the first cases reported in which nondiabetics had symptoms identical with the reaction observed in diabetics from overdoses of insulin (induced hyperinsulinism) the condition was called hyperinsulinism.^{7c} A year later Cammidge¹⁰ reported two cases of "hypoglycemia" which he assumed was due to defective glycogenesis by the liver. In November 1924 Jonas¹¹ cited a case of "hypoglycemia" reported by Hartman and Rieman, and reported another case, that of a diabetic who, a number of days after insulin therapy was discontinued, died in hypoglycemia (blood sugar 0.040 per cent). Jonas suggested the term "spontaneous hypoglycemia" to describe such cases. In 1925 John^{12a} reported two cases of "hyperinsulinism," one of a diabetic and the other a nondiabetic, who had symptoms of hypoglycemia with low blood sugars. John concluded that "the phenomenon must be due to some irregularity, or oversensitiveness of the insulogenic regulating mechanism."

In 1927 Wilder, Allan, Power and Robertson¹³ first proved pathologically the existence of hyperinsulinism. Theirs also was the first reported case of hyperinsulinism due to a neoplasm of the islands of Langerhans in which there were recurring attacks of convulsions and unconsciousness. Their classical report of the case of a physician who died in hypoglycemia from an inoperable islet cell carcinoma, which they studied at autopsy, is perhaps the most important contribution to the literature on hyperinsulinism. Finney and Finney¹⁴ in 1928 reported the first successful resection of a large portion of the pancreas for hyperinsulinism (fasting blood sugar 0.030 per cent). The pancreas was normal in appearance and microscopic section

showed normal islet cells. The patient's blood sugar was higher after the operation, but for a time she had psychic symptoms, though she was greatly benefited by the operation. Dr. Finney states five years after the operation that she is in good health. Pribram¹⁵ in 1928 reported three cases of "chronic hypoglycemia" and he suggested the term "glycopenia" as descriptive of such cases. Allan¹⁶ in 1929 reported two cases of "hyperinsulinism" in which there was hypoglycemia with convulsions and unconsciousness. Resection of a portion of the pancreas by Judd¹⁷ in one of Allan's cases resulted in improvement to the extent that the hypoglycemic symptoms were milder. Hartmann¹⁸ in January 1929 reported a case of "idiopathic hypoglycemia" in a negro who died in a state epileptic institution. Winans¹⁹ in 1928 reported three cases of "chronic hypoglycemia" in obese patients, which he ascribed to "overactivity of the pancreas." Waters²⁰ in 1929 reported three cases of "spontaneous hypoglycemia."

Carr, Parker, Grave, Fisher and Larrimore²¹ in August 1931 reported a case of "hyperinsulinism" in which the hypoglycemia (blood sugar 0.042 per cent) was associated with recurring attacks of unconsciousness and convulsions. Removal of a pancreatic adenoma cured the patient. Gammon and Tenery²² in 1931 reported a case of "hypoglycemia," "due to hyperinsulinism" and they suggested the term "dysinsulinosis" as descriptive of the condition. Marsh²³ in 1930 reported nine cases of mild "hyperinsulinism." Phillips²⁴ in 1931 reported a case of "hypoglycemia" in which autopsy revealed hyperplasia of the islands of Langerhans thus suggesting an organic basis for hyperinsulinism in one patient who did not have adenoma of the pancreas. A number of other cases have been reported by American clinicians, some using the term hyperinsulinism and others hypoglycemia, with various qualifying words. Derick²⁵ more recently reported a case of "spontaneous hyperinsulinism" due to an islet cell adenoma, in which the patient was cured by operation. Evarts Graham and Womack²⁶ up to December 1933 had successfully operated upon four adenomas of the pancreas, and had resected the pancreas in three additional cases of "hypoglycemia" in which adenomas were not found.

Most of the British clinicians who have reported cases, follow the lead of Cammidge, and use the term chronic hypoglycemia. Cammidge^{10c} considers that chronic infections of the liver and pancreas play an important rôle in the etiology of hypoglycemia, because, as he says: "Chronic catarrh of the upper intestines is generally associated with an infection of the bile and pancreas ducts, and the consequent disturbance of the liver and pancreas may contribute to the production of a low blood sugar."

Wauchope,²⁷ in one of the most comprehensive reviews of the general subject of "hypoglycemia" that has been published, employs the terms "spontaneous hypoglycemia," and "functional hyperinsulinism." Wauchope's bibliography on the subject of hypoglycemia and hyperinsulinism in all its phases is one of the most extensive in the literature on this new disease entity.

Moore,²⁸ of Dublin, reported a case of "spontaneous hypoglycemia" which he considered as due to "insulinism." Sippe and Bostock²⁹ in a recent number of the *Australian Medical Journal* reported 25 cases of "hypoglycemia" and in their excellent survey they describe as "true hypoglycemia," the "fulminating types" ((a) confusional or comatose, (b) epileptiform, (c) abdominal, (d) migrainous, (e) asthmatic, (f) vertiginous, (g) cardiac) and "chronic hypoglycemia." Sippe and Bostock consider "hypoglycemia" practically as common as hyperglycemia. In a large series of cases met with in general practice (in Brisbane, Australia) the "percentage of cases of hypoglycemia was 0.47 and that of diabetes 0.51."

The first book to be written on hypoglycemia and hyperinsulinism was by a Frenchman, Jean Sigwald, entitled "L'Hypoglycémie,"³⁰ with a foreword by Professor M. Rathery. In its 320 pages this very excellent monograph covers the literature up to 1932 on the various phases of hypoglycemia, including "spontaneous hypoglycemia," "experimental hypoglycemia," i.e., in animals by the use of insulin, and "hyperinsulinism"—"hypoglycémie par hyperpancréatic."

Most of the German medical writers who have reported cases, as Krause,³¹ use the word "hyperinsulinism." One of the most comprehensive papers that has been written on the subject is by Professor Max Rosenberg³² of Berlin on artificial and spontaneous hyperinsulinism, in which he brings out definitely that the manifestations of hyperinsulinism induced by giving excessive doses of insulin to animals and men are the same as those which occur in "spontaneous hyperinsulinism." It is interesting to note in the 141 references in Rosenberg's article how thoroughly he has covered the American literature on hyperinsulinism.

The only reference found in the Italian literature was the report of a case of "spontaneous hyperinsulinism" by Stief.³³ Three references have been found in the Scandinavian literature, one by Hagedorn³⁴ in which he reports two mild cases of "spontaneous hypoglycemia"; one by Ehrstrom³⁵ in which he reports a case of "chronic pancreatitis with hyperinsulinism"; and a third by Sjögren and Tillgren³⁶ who, in discussing the confusional or manic states observed in a case in which there was hypoglycemia, use the word "insulinism" to convey the idea of an excessive secretion of insulin by the pancreas.

It is evident from the various words and terms that have been used to describe the disorder due to the uninhibited, or excessive, secretion of insulin that there is need for a clarifying classification and nomenclature on this disease entity.

Spontaneous Hypoglycemia or Hyperinsulinism? It has been suggested that "for the present it would seem more in accordance with our actual lack of knowledge to designate all cases of hypoglycemia in which no definite proof of cause exists as spontaneous or idiopathic hypoglycemia rather than as cases of hyperinsulinism,"³⁷ reserving the word hyperin-

sulinism for the cases of hypoglycemia in which operation, or autopsy, proves the diagnosis.

If this criterion were held necessary for diagnosis in all internal diseases, few diagnoses would be made before operation or autopsy. Apply the criterion of "proof and cause" and few cases could be diagnosed as diabetes mellitus, because, as is well known, in many cases of diabetes even the autopsy shows no demonstrable lesion of the pancreas, or other organs that may be concerned in producing hyperglycemia; yet with very few exceptions, authorities on diabetes agree that the pancreas is the essential organ involved. Except in rare cases, whenever the diagnosis of diabetes is made it is assumed that there is a deficient secretion of insulin, and no one questions the diagnosis. Why should there be a different criterion for assuming a diagnosis of hyperinsulinism in the opposite secretory disorder of the pancreas when there is hypoglycemia with symptoms that are identical with those which have been repeatedly produced by the hypodermatic administration of insulin (induced hyperinsulinism)?

It is also granted that uncontrolled release of glycogen from the liver may be a factor in hyperglycemia just as deficient glycogenesis will result in hypoglycemia; but Mann³⁸ has shown that it requires massive destruction of the liver to produce hypoglycemia. Mann found that permanent reduction of hepatic tissue to less than 15 per cent resulted in only slight changes in the blood sugar level. Therefore, with such enormous reserve glycogenic power it does not seem likely that in functional disorders of the liver there will be enough impairment of function to produce hypoglycemia, without other evidences of liver disorder. It, therefore, would seem that the diagnosis of hyperinsulinism is justified in those cases of spontaneous hypoglycemia in which there is no evidence of disease of the liver, pituitary, suprarenal or thyroid glands. However, the possible involvement of other endocrine organs should never be forgotten in any case in which spontaneous hypoglycemia is a manifestation, and the search for such involvement should continue as long as the patient is under observation.

Even in cases of disturbed carbohydrate metabolism due to polyglandular dysfunction the disorder should be given a name that connects it with the organ that is predominantly involved; and at this time few will question that the pancreas is the most important, if not the essential, organ in the production of the symptoms of spontaneous hypoglycemia. The term hyperinsulinism would seem to be appropriate to use in the hypoglycemia resulting from hypopituitarism, because it is a generally accepted theory that the pituitary gland controls the secretion of insulin, and when there is hypopituitarism the secretion of insulin is uninhibited and hyperinsulinism results. Cushing in a recent personal communication to the author writes: "Unquestionably all the old states that we originally described as hypophysiopriva in dogs after hypophysectomy were due to hyperinsulinism though we had no means of determining this in years gone by."

DYSINSULINISM

The name dysinsulinism was coined to characterize a condition, or disease, in which there are at times manifestations of deficient insulin secretion—diabetes mellitus (hypoinsulinism); and at other times symptoms of hyperinsulinism. In other words the term dysinsulinism is intended to describe cases in which there is unregulated, uncontrolled, or irregular, secretion of insulin, with symptoms resulting at one time from hyperglycemia and at another time from hypoglycemia.

In the nomenclature of other endocrine glands in which there is irregular or uncontrolled secretion, with both hyper and hypo phases, the prefix *dys* is commonly used, as dyspituitarism, dysthyroidism and dysadrenia. Certainly no one would dispute the correctness of the term dyspituitarism as coined by Cushing; and no one would question that there are phases of hyperpituitarism and hypopituitarism in the same patients. That the hyperpituitary syndrome frequently is followed by hypopituitary manifestations in the same patient and the latter symptoms controlled by the use of pituitary opotherapy is an accepted fact.

Rowe² states that he frequently has seen hypothyroidism follow hyperthyroidism, and other endocrinologists have made similar observations. The term dysthyroidism is in general use and it is found in recent editions of medical dictionaries. Dysadrenia, likewise, is an accepted word in medical dictionaries and is used by authorities on adrenal disorders. It certainly does not require much imagination to believe that there is at times irregular, or uncontrolled, secretion of the islands of Langerhans; and that in such cases there should be symptoms of diabetes and hyperinsulinism in the same patients at different times. Certainly in making glucose tolerance tests on such patients the fasting blood sugar is sometimes abnormally low, but after the ingestion of one and one half grams of dextrose per kilo of body weight there is hyperglycemia for two or three hours to be followed by hypoglycemia accompanied by typical symptoms of an insulin reaction.

The need for the term dysinsulinism was felt in January 1924^{7a} when a woman came under our observation with a history of having had diabetes for one and a half years, but showing at the time of our examination hypoglycemia with symptoms of psycho-neurasthenia. She complained particularly of "spells of quivering, with weakness and a disturbed feeling" from midnight to about 2:00 a.m. She had learned that she could get relief from the attacks by taking food; and for several months she had kept an orange on her bedside table to eat when she awakened in the night with the "spells." Her fasting blood sugar was 0.047 per cent. This patient had been on an undernutrition diet for diabetes when her nervous symptoms developed. She had reduced in weight from 210 to 160 pounds. It seems probable that the undernutrition diet this patient had been using from July 1922 to January 1924 was a precipitating factor in upsetting the insulin regulatory mechanism of the pancreas.

Joslin,³⁰ in 1921, called attention to the occurrence of "spontaneous hypoglycemia" in diabetics on the undernutrition diet. He reported the deaths of two diabetics that occurred while on a very low carbohydrate diet, in which the blood sugar dropped to very low levels shortly before death, i.e., 0.050 and 0.040 per cent. In commenting on these two cases he said: "The discovery of the presence of hypoglycemia during the course of treatment (of diabetes) by undernutrition is a danger signal of the first importance." It seems probable that if Joslin had seen these cases after the discovery of insulin he would have suspected that the hypoglycemia was due to the excessive secretion of insulin; and since the patients had proved diabetes, due to the deficient secretion of insulin, what term is more appropriate to describe the condition than dysinsulinism? In the last few years several similar cases have been reported and the low blood sugars have been attributed to hypersecretion of insulin (Jonas,¹¹ John,^{12b} and Harrop⁴⁰).

In 1930 Howland, et al.⁴¹ reported a case of "dysinsulinism" in which there were attacks of convulsions and minor attacks resembling petit mal, and in which at times during a 24 hour study the blood sugar levels were low, 0.040, 0.041, 0.045 and 0.050 per cent. A glucose tolerance test showed a diabetic curve, i.e., 0.08, 0.25 and 0.24 per cent. They therefore pronounced it a case of dysinsulinism. Removal of a small carcinoma located at about the middle of the pancreas cured the patient clinically and the blood sugar readings had been normal for some time when the case was reported.

Nielsen and Eggleston⁴² in 1930 reported three cases of "dysinsulinism," with fasting blood sugar levels of 0.050, 0.069 and 0.064 per cent. Two of these cases were completely relieved by frequent feedings and the administration of suprarenal gland orally. The third patient was improved on the same diet.

Gammon and Tenery²² in 1931 reported the case of a woman who had attacks of unconsciousness and bizarre nervous symptoms which had been called "nerves" by several physicians. Her fasting blood sugar was 0.050 per cent. A sugar tolerance test was as follows: Fasting 0.050 per cent; in 45 minutes 0.225 per cent; in two hours 0.25 per cent. There was no sugar in her urine at any time. She was relieved by diet with frequent feedings; and a year later her fasting blood sugar was still low, 0.047 per cent, but her glucose tolerance curve was nearly normal, i.e., in 45 minutes 0.125 per cent, and in two hours and 45 minutes 0.111 per cent. Gammon and Tenery suggested the term "dysinsulinosis" as descriptive of the condition of unregulated insulin secretion.

The case of "dysinsulinism" reported in 1931 by Weil⁴³ was most dramatic. A woman aged 29 had been overweight and developed diabetes. On a low diet the sugar disappeared from her urine but she developed attacks of convulsions and unconsciousness during her menstrual periods. She had been pronounced an epileptic. Weil found a very low fasting blood sugar

reading, 0.037 per cent. On a high carbohydrate diet with considerable quantities of sugar her blood sugar readings fell to zero, or at least so low that the colorimeter could not be read. Her diet was changed to a relatively low carbohydrate and high fat diet with frequent feedings, and her "epilepsy" has been cured. She has not had a convulsive attack in more than a year. Her recent fasting blood sugar readings were normal, i.e., 0.090, and 0.085 per cent.

More recently Love⁴⁴ reported a case in which the blood sugar readings were irregular, at times low, when the hypoglycemic manifestations were pronounced, and at other times high, when he had diabetic symptoms. An adenoma of the pancreas was suspected. Love diagnosed his case "dysinsulinism."

The above facts regarding reported cases in which patients showed evidences of uncontrolled or irregular insulin secretion, with hypoglycemia alternating with hyperglycemia, seem to justify the diagnosis of dysinsulinism as made by the authors quoted.

HYPOGLYCEMIA

Hypoglycemia, a low concentration of sugar in the blood, is a condition—not a disease—resulting from dysfunction, or pathologic changes in the liver, or in the organs of the internal secretion concerned with carbohydrate metabolism, including the pancreas, the suprarenals, the thyroid, and the pituitary bodies. Hypoglycemia due to whatever cause, is associated with more or less characteristic symptoms depending to a great extent upon the degree of subnormal blood sugar concentration.

It is generally agreed by clinicians that the normal blood sugar concentration ranges between 80 and 120 mg. per 100 c.c. of blood. Usually no symptoms of hypoglycemia are observed until the blood sugar falls below 0.070 per cent, but below that point and to 0.060 per cent the patient complains of protean symptoms, the most characteristic of which are those described by Banting⁴ and MacLeod⁵ as occurring from an overdose of insulin, i.e., hunger, weakness, trembling, sweating and nervousness.

A great variety of symptoms^{7c} has been described by various observers as occurring in patients with moderately low blood sugars. They include dizziness, vertigo, headaches, irritability, attacks of petit mal, lassitude, fainting attacks, tachycardia, the fatigue syndrome, the anxiety neuroses, emotional disturbances, hysterical attacks and muscular twitchings. The symptoms in different patients are at times so bizarre that they cannot be classified, the only common clinical findings being a moderately low blood sugar (from 0.060 to 0.050 per cent), and the observation that the attacks occur three or four hours after meals, particularly during the early hours before breakfast. The symptoms are relieved by taking food, and prevented by frequent feedings before the hours of expected attacks.

The symptoms of the severe degrees of hypoglycemia (blood sugar usually below 0.050 per cent) are more constant. There may be recurring

periods of mental lapses, or even psychotic symptoms, unexplained attacks of unconsciousness, muscular twitchings, and often convulsions.^{7d} A number of such cases have been diagnosed, erroneously, as epilepsy, and even insanity. Recovery in such attacks may occur spontaneously, but more rapidly after the oral or parenteral administration of dextrose solutions. Coma and death may be the outcome in the most severe cases.

While hypoglycemia may be due to a functional disorder, or pathological changes in a number of endocrine glands, like its antithesis hyperglycemia, it is a clinical finding that occurs usually in the disturbed secretion of the islands of the pancreas. It should be stressed, however, that the presence of hypoglycemic symptoms in a patient with low blood sugar readings does not necessarily mean that he has hyperinsulinism; because hypoglycemia may result from deficient glycogenesis in the liver, from poisons, such as arsenicals, particularly arsphenamine, as in the case described by Cross and Blackford.⁴⁵ Other hepatotoxins as phenylhydrazine, phosphorus and the toxin of mushroom poisoning may result in such extensive damage to the liver as to disturb its glycogenic function. Likewise, acute yellow atrophy of the liver and massive tumors of the liver as in the case reported by Nadler and Wolfer⁴⁶ may cause marked hypoglycemia. Cammidge^{10e} in his report of 200 cases of mild hypoglycemia considers that disturbed liver function is the important factor.

The adrenals control the mobilization of glycogen and a deficient secretion of the suprarenal glands may result in varying degrees of hypoglycemia. Anderson's⁴⁷ case in which a man had recurring attacks of hypoglycemic coma, finally dying in one, and in which the autopsy revealed a carcinoma of the cortex of the left suprarenal gland, is a striking illustration of the fact that adrenal disease can cause a severe and even fatal hypoglycemia. Rabinovitch and Barden⁴⁸ recently reported a case in which the patient died in hypoglycemic coma (blood sugar 0.025 per cent) and which at autopsy showed that the medullary portion of both adrenals was entirely replaced by lymphoid tissue. Evidently there was no secretion of adrenin. There was also a small nodule of inflammatory tissue on the tail of the pancreas, but hypoadrenalinism was considered as the important etiological factor in the hypoglycemia.

Addison's disease, of which adrenal pathology is the essential factor, is associated with hypoglycemia (Wadi,⁴⁹ and Porges⁵⁰). Stenström⁵¹ in 1926, reported the case of a woman who had a pronounced fatigue syndrome and unconsciousness associated with hypoglycemia. Immediate return to consciousness followed the hypodermatic administration of adrenalin. Stenström thought his case due to hyperinsulinism and hypoadrenalism. Having observed low blood pressure in some of our first cases in 1923 and 1924 we thought that while hyperinsulinism was the most important cause of the hypoglycemic symptoms, yet we considered it possible that hypoadrenalism may have been a factor in producing the abnormally low blood sugars in the cases. Ten years' experience in treating many cases of hyper-

insulinism further convinces us that hypoadrenalism not infrequently is associated with the hypoglycemia of hyperinsulinism and that it may be a factor in producing the hypoglycemia.

Thyroid deficiency (hypothyroidism) because of decreased metabolism, with insufficient utilization of glycogen, may result in hypoglycemia (Zubiram⁵²). Holman⁵³ stressed the seriousness of the hypoglycemia, sometimes producing unconsciousness, that may appear 24 to 36 hours following operation for hyperthyroidism; and noted the immediate relief in such cases that follows the intravenous administration of glucose.

Years ago Cushing⁵⁴ called attention to hypoglycemia associated with hypophyseal tumors (hypopituitarism). More recently Joseph Wilder⁵⁵ has described what he thinks is a distinct entity, which he calls hypopituitary hypoglycemia. The gonads perhaps through their pituitary relations may be a factor in producing low sugar concentration. Weil's⁴³ case of the woman who had hypoglycemic convulsions only during menstruation illustrates that type.

Pluriglandular pathology, or dysfunction or hypofunction of two or more of the endocrine glands, may cause hypoglycemia, as in Patterson's⁵⁶ case of a woman who died in hypoglycemic coma. The autopsy showed a very small hypophysis and atrophy of the thyroid, adrenals and ovaries with what appeared to be a normal pancreas. Gougerot and Peyre⁵⁷ reported several cases of hypoglycemia which they thought were due to "hypoadrenalemia and dysinsulinism."

Since all types of hypoglycemic symptoms from the mildest to the most severe in which there are convulsions and coma have been produced by the injection of insulin (induced hyperinsulinism) without any other factor that could produce hypoglycemia, it surely seems that hyperinsulinism is the one most frequent cause of spontaneous hypoglycemia. Therefore, unless there are evidences of hypofunction of the other endocrine glands that play a part in carbohydrate metabolism, what has been called iodopathic, or spontaneous, hypoglycemia may safely be classified as being due to the excessive secretion of insulin by the islet cells of the pancreas (hyperinsulinism).

Even in the event that other endocrine glands are involved, certainly in all except a few cases the relatively or actually excessive secretion of insulin is the dominant factor, therefore the primary diagnosis should be hyperinsulinism; and hypoadrenalism, hypothyroidism or hypopituitarism should be added as a secondary diagnosis.

It surely seems that hypoglycemia bears the same relationship to hyperinsulinism that hyperglycemia does to diabetes mellitus (hypoinsulinism). No one would think of reporting a case of diabetes (hypoinsulinism) as hyperglycemia; neither should hypoglycemia be employed in reporting a case in which there is a low blood sugar, with the usual symptoms that may occur in hyperinsulinism.

The Quarterly Cumulative Index Medicus very properly lists hypoglycemia under the heading of blood sugar, and not as a disease entity; and it lists hyperinsulinism under diseases of the pancreas. The recently published "Standard Classified Nomenclature of Disease"¹ which is the guide for nomenclature in all teaching hospitals, does not recognize the term hypoglycemia as a diagnosis; but it accepts, and lists, hyperinsulinism as a disease under the heading of disorders of carbohydrate metabolism.

Dr. Lewellys F. Barker, Professor Emeritus of Medicine, Johns Hopkins University, noted for his accuracy in the use of words, in his new book (1934) on "Treatment of the Commoner Diseases Met with by the General Practitioner,"² classifies "hypoinsulinism (diabetes mellitus)" and "hyperinsulinism" as endocrinopathies under the subtitle of "commoner disorders of the function of internal secretion of the pancreas." When such an ardent and discriminating philologist as Dr. Barker uses the term hypoinsulinism as synonymous with diabetes mellitus, and the word hyperinsulinism in the nomenclature of the disorders of insulin secretion, no other authority is needed for their usage by the medical profession.

Considering the data relating to the nomenclature and classification of the disorders of insulin secretion that have been presented, the use of the words hypoinsulinism (diabetes mellitus), hyperinsulinism and dysinsulinism in the terminology of the disorders of insulin secretion is logical and philologically correct.

CONCLUSIONS

1. There is need for a clarifying classification of the secretory disorders of the islands of Langerhans of the pancreas; and the methods of nomenclature adopted in naming the disorders of other endocrine glands, i.e., the thyroid, the pituitary glands, and the suprarenal glands, should be applied in the terminology of the endocrine disturbances of the pancreas.

2. Diabetes mellitus, with few reservations, may be regarded as essentially due to an absolute, relative, or qualitative deficiency of insulin, and therefore is synonymous with, but never should be replaced by, the term hypoinsulinism.

3. Whereas it is unusual clinically to observe cases in which permanent hyperglycemia, polyuria, and glycosuria are solely or largely due to discoverable excessive secretion of the pituitary, thyroid, and adrenal glands, theoretically such cases may occur; and if recognized they should be diagnosed as pituitary diabetes, thyroid diabetes or adrenal diabetes, depending upon the dominant endocrine factor involved.

4. Hyperinsulinism best defines the disease entity characterized by hypoglycemia and resulting from an imbalance of those factors which, acting with the islands of Langerhans, ordinarily maintain the level of blood sugar within normal limits, whether the symptoms are mild, moderately severe, or severe.

5. Dysinsulinism is the term which best describes the condition in which there is irregular, unregulated or uncontrolled, insulin activity; with hyperglycemia alternating with hypoglycemia, in patients who have at times symptoms of diabetes, and at other times symptoms due to hypoglycemia not induced by exogenous insulin.

6. Hyperglycemia and hypoglycemia are not disease entities, but are temporary conditions of the blood resulting from pathological or functional changes in one or more of the organs concerned in carbohydrate metabolism. Hyperglycemia is not synonymous with diabetes and should not be used in reporting cases of illness due to deficient secretion of insulin. Neither is hypoglycemia synonymous with hyperinsulinism, and its use in reporting cases ascribed as due to the excessive secretion of insulin should be discouraged.

7. The anti-insulin action of the pituitary, thyroid and adrenal glands is an acceptable theory, but spontaneous hyperinsulinism due to conditions other than absolute or relative overactivity of the pancreas seems as difficult to prove clinically as hyperglycemia of extra-pancreatic origin. Therefore, the diagnosis of hyperinsulinism seems justifiable and advisable, in patients with hypoglycemic symptoms in whom there is no evidence of disease of the liver, thyroid, hypophysis or adrenals.

8. Even when there is multiglandular involvement in a patient with hypoglycemic symptoms, since it seems likely that in all except a few unusual cases the pancreas is the most important organ involved, the diagnosis should be hyperinsulinism, with a secondary diagnosis carrying the name of the disorder of the hypophysis, the thyroid, or the adrenals, that may also be present. In the very rare cases in which another organ is the dominant factor in producing the hypoglycemia the diagnosis of hyperinsulinism without qualification is not justifiable.

BIBLIOGRAPHY

1. A standard classified nomenclature of disease, H. B. Logie, Editor, 1933, The Commonwealth Fund, New York.
2. ROWE, A. W.: The differential diagnosis of endocrine disorders, 1932, Williams and Wilkins, Baltimore, pp. 117-118.
3. BANTING, F. G., and BEST, C. H.: Internal secretions of pancreas, Jr. Lab. and Clin. Med., 1922, vii, 251-266.
4. BANTING, F. G., CAMPBELL, W. R., and FLETCHER, A. A.: Clinical experience with insulin in diabetes, Brit. Med. Jr., 1923, i, 8-12.
5. NOBLE, E. C., and MACLEOD, J. J. R.: The influence of sugars and other substances on the toxic effects of insulin, Am. Jr. Physiol., 1923, lxiv, 547-560.
6. SCHAFFER: The endocrine organs, Longmans Green and Co., p. 125. Cited by Joslin,^{9a} page 33.
7. HARRIS, S.: (a) Hyperinsulinism and dysinsulinism, Jr. Am. Med. Assoc., 1924, lxxxiii, 729-733. (b) Epilepsy and narcolepsy associated with hyperinsulinism, Jr. Am. Med. Assoc., 1933, c, 321-328. (c) Hyperinsulinism and dysinsulinism (insulogenic hypoglycemia), with chronological review of cases reported in United States and Canada, Endocrinology, 1932, xvi, 29-42. (d) Hyperinsulinism and epilepsy, South. Med. Jr., 1933, xxvi, 1026-1033. (e) Hyperinsulinism, a definite disease entity, Jr. Am. Med. Assoc., 1933, ci, 1958-1965.

8. WHITE, P.: Diabetes in childhood and adolescence, 1932, Lea and Febiger, Philadelphia.
9. JOSLIN, E. P.: The treatment of diabetes mellitus, 4th ed., 1928, Lea and Febiger, Philadelphia, (a) page 99; (b) page 732.
10. CAMMIDGE, P. H.: (a) Hypoglycemia, *Lancet*, 1924, ii, 1277-1279. (b) Chronic hypoglycemia, *Practitioner*, 1927, cxix, 102-112. (c) Chronic hypoglycemia, *Brit. Med. Jr.*, 1930, i, 818-822.
11. JONAS, L.: Hypoglycemia, *Med. Clin. N. Am.*, 1924, viii, 949-958.
12. JOHN, H. J.: (a) Hyperinsulinism, *Ohio State Med. Jr.*, 1925, xxi, 99-100. (b) Hyperinsulinism, *Surg., Gynec. and Obst.*, 1927, xlv, 190-193.
13. WILDER, R. M., and others: Carcinoma of islands of pancreas; hyperinsulinism and hypoglycemia, *Jr. Am. Med. Assoc.*, 1927, lxxxix, 348-355.
WILDER, R. M.: Hyperinsulinism, *Internat. Clin.*, 1933, ii, 1-18.
14. FINNEY, J. M. T., and FINNEY, J. M. T., JR.: Resection of pancreas, *Ann. Surg.*, 1928, lxxxviii, 584-592.
15. PRIBRAM, E.: Chronic glycopenia; clinical picture, analysis of its causes and suggestions for its therapy, *Jr. Am. Med. Assoc.*, 1928, xc, 2001.
16. ALLAN, F. N.: Hyperinsulinism; report of two cases, *Arch. Int. Med.*, 1929, xlv, 65-70.
17. ALLAN, F. N., BOECK, W. C., and JUDD, E. S.: Surgical treatment of hyperinsulinism, *Jr. Am. Med. Assoc.*, 1930, xciv, 1116-1119.
18. HARTMANN, F. L.: Hypoglycemia, *Med. Clin. N. Am.*, 1929, xii, 1035-1046.
19. WINANS, H. M.: Chronic hypoglycemia, *South. Med. Jr.*, 1930, xxiii, 402-406.
20. WATERS, W. C., JR.: Spontaneous hypoglycemia; rôle of diet in etiology and treatment, *South. Med. Jr.*, 1931, xxiv, 249-252.
21. CARR, A. D., and others: Hyperinsulinism from B-cell adenoma of pancreas; operation and cure, *Jr. Am. Med. Assoc.*, 1931, xcvi, 1363-1367.
22. GAMMON, G. D., and TENERY, W. C.: Hypoglycemia; clinical syndrome, etiology and treatment; report of case due to hyperinsulinism, *Arch. Int. Med.*, 1931, xlvii, 829-854.
23. MARSH, H. E.: Hyperinsulinism; with report of case, *Wisconsin Med. Jr.*, 1931, xxx, 340-343.
24. PHILLIPS, A. W.: Hypoglycemia associated with hypertrophy of islands of Langerhans, *Jr. Am. Med. Assoc.*, 1931, xcvi, 1195-1198.
25. DERICK, C. L., and others: Spontaneous hyperinsulinism; report of case of hyperinsulinism cured by surgical intervention, *New Eng. Jr. Med.*, 1933, ccviii, 293-298.
26. GRAHAM, E. A., and WOMACK, N. A.: Application of surgery to hypoglycemic state due to islet tumors of pancreas and to other conditions, *Surg., Gynec. and Obst.*, 1933, lvi, 728-742; and personal communications.
27. WAUCHOPE, G. M.: Hypoglycemia; critical review, *Quart. Jr. Med.*, 1933, ii, 117-156.
28. MOORE, H., O'FARRELL, W. R., MALLEY, L. K., and MORIARTY, M. A.: Acute spontaneous hypoglycemia, *Brit. Med. Jr.*, 1931, ii, 837-840.
29. SIPPE, C., and BOSTOCK, J.: Hypoglycemia: survey and account of 25 cases, *Med. Jr. Australia*, 1933, i, 207-218.
30. SIGWALD, J.: (a) L'hypoglycémie, 1932, Gaston Doin, Paris. (b) Les hypoglycémies spontanées, *Paris méd.*, 1932, ii, 321-332.
31. KRAUSE, F.: Hyperinsulinismus mit hypoglykämischen symptomkomplex, *Klin. Wchnschr.*, 1930, 2346-2349.
32. ROSENBERG, M.: Über artefiziellen und spontanen Hyperinsulinismus, *Klin. Wchnschr.*, 1932, xi, 2097-2103.
33. STIEF, S.: L'iperinsulinismo spontaneo, *Riv. di pat. nerv.*, 1932, xxxix, 139-144.
34. HAGEDORN, H. C.: Spontaneous hypoglycemia, *Acta med. Scandinav.*, 1932, Supp., 187-195.
35. EHRSTROM, R.: Ein Fall von chronischer Pankreatitis mit Hyperinsulinismus, *Acta med. Scandinav.*, 1932, lxxvii, 334-338.
36. SJÖGREN, T., and TILLGREN, J.: Peculiar states of confusion in insulinism, *Acta med. Scandinav.*, 1927, lxxv, 684-696.

37. Spontaneous hypoglycemia versus hyperinsulinism, Editorial, *Ann. Int. Med.*, 1933, vi, 1507-1510.
38. MANN, F. C.: Effects of complete and partial removal of liver, *Medicine*, 1927, vi, 419-511.
39. JOSLIN, E. P.: Practical lessons for physicians and patients in diabetes, *Med. Clin. N. Am.*, 1921-22, iv, 1723.
40. HARROP, G. A., JR.: Hypoglycemia and toxic effects of insulin, *Arch. Int. Med.*, 1927, xl, 216-225.
41. HOWLAND, G., CAMPBELL, W. R., MALTBY, E. J., and ROBINSON, W. L.: Dysinsulinism: convulsions and coma due to islet cell tumor of the pancreas, with operation and cure, *Jr. Am. Med. Assoc.*, 1929, xciii, 674-679.
42. NIELSEN, J. M., and EGGLESTON, E. L.: Functional dysinsulinism with epileptiform seizures; treatment, *Jr. Am. Med. Assoc.*, 1930, xciv, 860-863.
43. WEIL, C. K.: Functional hyperinsulinism; epileptiform convulsions accompanying spontaneous hypoglycemia, *Internat. Clin.*, 1932, xlii, 33-50.
44. LOVE, J.: Dysinsulinism: discussion and case report, *Jr. Am. Med. Assoc.*, 1933, c, 814-816.
45. CROSS, J. B., and BLACKFORD, L. M.: Fatal hepatogenic hypoglycemia following neoarsphenamine, *Jr. Am. Med. Assoc.*, 1930, xciv, 1739-1743.
46. NADLER, W. H., and WOLFER, J. A.: Hepatogenic hypoglycemia associated with primary liver cell carcinoma, *Arch. Int. Med.*, 1929, xlii, 700-710.
47. ANDERSON, H. B.: Tumor of adrenal gland with fatal hypoglycemia, *Am. Jr. Med. Sci.*, 1930, clxxx, 71-79.
48. RABINOVITCH, J., and BARDEN, F. W.: Hypoglycemia associated with tumor of islands of Langerhans and with adrenal insufficiency, *Am. Jr. Med. Sci.*, 1932, clxxxiv, 494-503.
49. WAD, W.: Über Hypoglykämie bei Morbus Addisonii, *Klin. Wchnschr.*, 1928, vii, 2107-2109, cited by Cross and Blackford.⁴⁵
50. PORGES, O.: Über Hypoglykämie bei Morbus Addison sowie bei nebennierenlosen Hunden, *Ztschr. f. klin. Med.*, 1910, lxi, 341.
51. STENSTRÖM, T.: (a) Some observations on spontaneous hypoglycemia, *Acta med. Scandinav.*, Supp. 26, 170. (b) Spontane hypoglykämische Reaktion bei stillender Frau, *Deutsch. Arch. f. klin. Med.*, 1926, cliii, 181-189.
52. ZUBIRAM, S.: Sobre un caso de hipoglicemia, *Med. Mexico*, 1929, ix, 306-310.
53. HOLMAN, E. F.: Hypoglycemia in exophthalmic goiter, *Bull. Johns Hopkins Hosp.*, 1923, xxiv, 69-70.
54. CUSHING, H.: The pituitary body and its disorders, 1912, J. B. Lippincott and Company, Philadelphia, page 261.
55. WILDER, J.: Ein neues hypophysäres Krankheitsbild: Die hypophysäre Spontanhypoglykämie, *Deutsch. Ztschr. f. Nervenhe.*, 1930, cxii, 192-250.
56. PATTERSON: A case of spontaneous hypoglycemic coma, *Acta med. Scandinav.*, 1928, lxi, 232.
57. GOUGEROT, H., and PEYRE, E.: Hypo-épinéphrie et dysinsulinisme; nouveau syndrome, *Compt. rend. Soc. de biol.*, 1925, xciii, 1202-1203.
58. BARKER, L. F.: Treatment of the commoner diseases met with by the general practitioner, 1934, J. B. Lippincott, Philadelphia, pages 293-299.

OBLITERATING THROMBOSIS OF THE PULMONARY ARTERIES *

By W. M. FOWLER, M.D., *Iowa City, Iowa*

OBLITERATING thrombosis of the pulmonary artery or its main branches is a relatively uncommon condition if those cases which occur as a complication of surgical procedures or the puerperal state are excluded. The incidence of the condition cannot be determined from the published reports which, for the most part, appear as pathological studies on single cases. Billings¹ found 16 cases in 6200 autopsies, an incidence of 0.26 per cent, and included only those in which he felt that an embolic origin had been excluded. Six cases were found in 935 consecutive autopsies at the University Hospital, including those associated with operative procedures and septicemia. No study of a large series has been made to determine the common etiological and semeiographic features and it is for this reason that the present case is reported and the available literature reviewed. A thorough search, with the collection of all reported cases, has not been attempted. Those reports which are concerned primarily with postoperative and postpartum cases have been omitted, as have those of multiple thrombosis of the smaller branches as reported by Frothingham.²

CASE REPORT

E. F., a white male, aged 52 years, was first admitted to the University Hospital in 1929 for a hemorrhoidectomy. At that time the heart and lungs were considered to be normal and the blood pressure was 145 systolic and 95 diastolic. His second admission was in July 1932 and at this time he gave a history of having had a dry cough and a little shortness of breath on exertion for a period of about 15 years. These had not prevented him from carrying on his usual activities until May 1932 when he began to have severe paroxysms of coughing which produced extreme dyspnea. These paroxysms were brought on by talking, exertion, or respiratory irritation. Soon after this exacerbation of symptoms he began to have an afternoon fever ranging from 101° to 103° (F.). At the time of admission he had an evening temperature of 100° (rectal) which subsided after three days' rest in bed and remained normal during the remainder of his stay in the hospital. He was not cyanotic or dyspneic except with the frequent paroxysms of coughing. A few transient râles were found at the base of the right lung but aside from this the cardio-respiratory system was considered normal. The blood pressure was 140 systolic and 100 diastolic. Roentgenological examination showed some enlargement of the right hilus area and fibrosis of both lung fields. Treatment for chronic bronchitis was instituted.

He returned to the hospital in October 1932 stating that both the shortness of breath and the cough had become worse and that it was necessary for him to sit upright in order to sleep. He had had nocturnal dyspnea on several occasions and at times a feeling of substernal oppression with occasional sharp pains at the right costal margin. He had also noted palpitation and tachycardia on slight exertion but there had been no edema of the extremities. The cough had never been productive.

* Received for publication September 22, 1933.

From the Department of Internal Medicine State University of Iowa, Iowa City, Iowa.

The patient was extremely dyspneic and cyanotic at the time of admission to the hospital. The heart was not enlarged and, in particular, there was no increased accessibility of the right ventricle. The blood pressure was 88 systolic and 70 diastolic, whereas it had been 140 systolic and 100 diastolic 10 weeks previously. The liver dullness extended 2 cm. below the costal margin. There was no ascites or peripheral edema.

He had a constant elevation of temperature throughout the period of hospitalization, which, on one occasion, reached 104.6° (rectal). Repeated blood cultures were sterile and agglutination tests for typhoid, paratyphoid and undulant fever were negative.

Roentgenograms showed an enlargement of both hilus regions with two small areas of increased density in the right lung suggestive of infiltrative lesions. These had not been present on the previous examination and were interpreted as being embolic in origin. They gradually regressed.

The electrocardiogram was that of a right axis deviation with sharply inverted T-waves in Leads II and III and some slurring of the QRS complex. The observed vital capacity was 4500 c.c., the theoretical being 4175 c.c.

The renal concentration tests, non-protein-nitrogen of the blood and basal metabolic rate were normal. The hemoglobin dropped from 98 to 77 per cent and the erythrocytes from 5,780,000 on admission to 4,410,000. The leukocytes ranged from 14,250 to 8,000 with a normal differential count.

The dyspnea gradually improved and the patient was able to sleep with no elevation of his head. The cough became less troublesome with only occasional mild paroxysms so that he was able to talk without producing either cough or dyspnea. The cyanosis diminished but did not completely disappear. In spite of the apparent



FIG. 1. Longitudinal section through the thrombosed right pulmonary artery showing the extension of the thrombus into the branches and atelectasis of the middle lobe.



FIG. 2. Cross section through the right pulmonary artery showing complete obliteration of the lumen by the organizing thrombus.

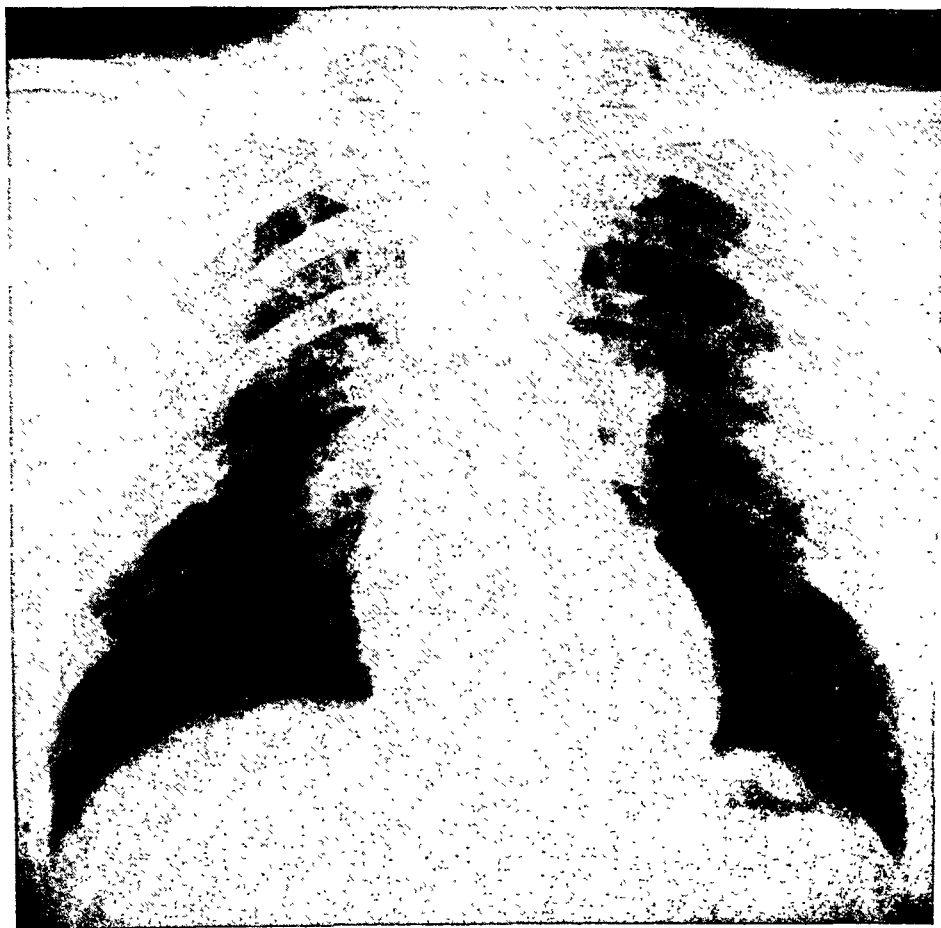


FIG. 3. Roentgenogram of chest showing dense hilus areas and a shadow in the region of the right pulmonary artery.

improvement the patient had a constant apprehensive attitude and facial expression. He was given permission to sit in a chair beside his bed but on the second occasion he suddenly became dyspneic, cyanotic and had a profuse, cold diaphoresis. He had two similar attacks within the next five hours, the third being fatal. Death occurred November 27, 1932, 46 days after admission to the hospital.

Necropsy: The right and left pulmonary arteries were occluded by separate thrombi which were adherent to the vessel walls. The proximal end of the thrombus in the right branch protruded into the pulmonary aorta but was not adherent in the latter region. Both thrombi extended into the branches of their respective arteries. The right pulmonary artery was completely occluded. While the thrombosis of the left pulmonary artery was not complete, the proximal end of the thrombus had apparently become loosened and folded over on itself so as to produce complete obstruction. Microscopic examination of the thrombi at various levels showed that they were firmly adherent to the vessel wall and had undergone organization. No atheromatous changes were found and the small vessels beyond the thrombi were normal. The vessel wall beneath the thrombus presented granulation and reparative fibroblastic tissue which replaced the entire thickness of the vessel wall in some sections. There were many inflammatory cells in these areas and polymorphonuclear cells were present in the more recent parts of the thrombi. The right lung weighed 800 gm., the left 620 gm. No areas of infarction were found. Both were markedly congested with only slight evidences of chronic inflammation in the large bronchi.

The heart weighed 400 gm. and the right auricle and ventricle were definitely dilated. No thrombi were found in the heart or peripheral vessels. A *Streptococcus viridans* grew in cultures taken from the thrombus. The remainder of the necropsy findings were unimportant.

COMMENT

This case presents a complete occlusion of the right pulmonary artery by thrombosis and a partial thrombotic occlusion of the left. The terminal event was apparently precipitated by a detachment of the proximal end of the left thrombus which permitted it to fold on itself and completely occlude the remaining portion of the left pulmonary artery. The apparent age of the thrombi on microscopic examination was compatible with the seven months' duration of symptoms. Even though antemortem blood cultures had been sterile, a positive culture was obtained from the thrombus at necropsy. This intravascular infection was undoubtedly the etiologic agent.

Two cases of pulmonary artery thrombosis were found associated with cardiac lesions. One of these presented the usual symptoms and findings of mitral stenosis with congestive heart failure but necropsy revealed an occluded pulmonary artery in addition to the valvular defect. The symptoms of the pulmonary occlusion had been entirely masked by the cardiac lesion and its presence had not been suspected. In the second case an active endocarditis was present and necropsy revealed a large vegetation on the tricuspid valve. The thrombus in the pulmonary artery was undoubtedly of embolic origin. It had produced no recognizable symptoms in the presence of the primary cardiac disease.

Septicemia was present in three additional cases. One followed an appendectomy at which a ruptured gangrenous appendix was found. The patient died suddenly on the ninth postoperative day and a thrombosis of the

TABLE I

Author	Sex Age	Vessel Occluded	Symptoms	Associated Pathology and Remarks
Rouslaquoix and Perri- mond ³	M. 57	Right main branch	Dyspnea, cyanosis, fever, cardiac de- compensation	Asthma, bronchiectasis, emphysema Hypertrophy of right ventricle Dilatation of pulmonary aorta
Lutembacher ⁴		Right main branch		Mitral stenosis
Barnes and Yater ⁵	M. 34	Both main trunks	Dyspnea, cough, pleural pain, cardiac decompensation	Bronchiectasis and adhesive pleuritis Hypertrophy of right ventricle Inverted T-wave in Leads II and III
Allbutt ⁶		Pulmonary aorta	Ashen pallor Distressed respiration	Occurred during recovery from pneumonia
Dickinson ⁷	M. 4½	Main trunk and pri- mary branches	Cyanosis Respiratory embarrassment	Congenital pulmonary stenosis and patent interventricular septum
Eiman ⁸	M. 81	Main trunk and right branch	Chill and weakness	Thrombus in right renal artery and ab- dominal aorta. Dilated right heart
Jump and Baumann ⁹ ...	M. 48	Main trunk and both main branches	Cyanosis, dyspnea, cough, edema. Sud- den exacerbation of symptoms 3 days before death	Hypertrophy of right heart and dilated pulmonary aorta Some pulmonary sclerosis EKG—right ventricular preponderance
Means and Mallory ¹⁰ ...	M. 60	Right branch	Cyanosis and dyspnea Fever and leukocytosis	Hypertrophied bronchial arteries Both ventricles hypertrophied
Ljungdahl ¹¹	F. 51	Right main branch	Cough for 12 years Cyanosis, dyspnea Cardiac decompensation	Right heart enlarged Sclerosis of larger pulmonary vessels
Ljungdahl ¹¹	F. 38	Right main branch	Cough for 8 years. Dyspnea and cya- nosis for 4 years. Severe for a few months.	Right ventricle hypertrophied Thrombosis of terminal branches on left. Syphilis

TABLE I—Continued

Author	Sex Age	Vessel Occluded	Symptoms	Associated Pathology and Remarks
Desclin and Regnier ¹² . . .	M. 53	Right main branch	Cough for 25 years	Right ventricle dilated
Desclin and Regnier ¹² . . .	M. 55	Both main branches	Dyspnea, cyanosis, fever, edema Cyanosis, dyspnea, cough, edema. Symptoms of 4 mos. duration with sudden exacerbation 15 days before death	Syphilitic aortitis Thrombophlebitis of right femoral, iliac veins and vena cava
Stadelmann ¹³	M. 27	Both main branches	Cyanosis, fever, cardiac decompensation	Sclerosis of pulmonary artery Mitral stenosis and insufficiency
Mönckeberg ¹⁴	M. 56	Main trunk and right branch. Separate thrombus in left branch	Weakness, cyanosis Cardiac decompensation	Hypertrophy of right ventricle Thrombus in vena cava Arteriosclerosis of pulmonary vessels
Richter ¹⁵				Coronary artery disease
Neumeister ¹⁶				Chlorosis
Westphal ¹⁷				
Ittameier ¹⁸		Right branch		Emphysema and pleural adhesions Aortic stenosis and insufficiency
Tugendreich ¹⁹				Tuberculosis with caseation, and tabes dorsalis
Neddersen ²⁰		Right and left branches		Mitral stenosis and insufficiency
Brenner ²¹	F. 58	Right branch and medium sized ves- sels	Chronic cough Cyanosis, dyspnea, and edema	Hypertrophy of right ventricle Changes in vessel wall
Brenner ²¹	F. 49	Right and left	Chronic cough, hemoptysis Cyanosis and dyspnea	Emphysema and bronchitis Changes in vessel wall

TABLE I—Continued

Author	Sex Age	Vessel Occluded	Symptoms	Associated Pathology and Remarks
Brenner ²¹	M. 58	Many smaller branches	Sudden onset 19 months previously	Coronary artery sclerosis
Brenner ²¹	M. 56	Branch to right lower lobe		Bronchitis and emphysema
Brenner ²¹	F. 46	Branch to right lower lobe	Dyspnea, cyanosis, edema	Atheroma of pulmonary artery
Brenner ²¹	M. 60	Branches to right upper and lower lobes	Dyspnea and fainting attacks	Mitral stenosis and atheroma of pulmonary artery
Goedel ²²	M. 59	Main trunk and right branch	Cyanosis, dyspnea, edema	Emphysema
Goedel ²²	M. 50	Medium sized branches	Cardiac failure	Atheroma of pulmonary artery
Hart ²³	F.	Main stem and both branches	Cyanosis, dyspnea, edema	Right ventricle enlarged
Hart ²³	M.	Main stem and right branch	Cardiac failure	Hypertrophy of right and left ventricles
Boswell and Palmer ²⁴ ...	M. 39	Right and left arteries	Dyspnea, malaise, fatiguability. Sudden exacerbation of dyspnea and cyanosis	Tabes dorsalis and pyelonephritis
Samek ²⁵	F. 63	Right and left branches	Dyspnea, cough, cyanosis	Thrombus in left crural vein
Billings ¹	M. 50	Both right and left branches	Weakness, pain in right chest of 10 days' duration	Bronchitis
Billings ¹	M. 60	Both branches	Dyspnea and edema, cough	Dilated right heart
				Right pleural effusion
				Thrombus of left renal and right femoral veins
				Bilateral hydrothorax, congestion and edema of lungs
				Chronic interstitial nephritis
				Infarcts in both lungs, chronic pleurisy.
				Hypertrophy and dilatation of heart

TABLE I—Continued

Author	Sex Age	Vessel Occluded	Symptoms	Associated Pathology and Remarks
Billings ¹	F.	Many vessels on right Not main trunks	Dyspnea, edema and cough	1 month postpartum at onset of symptoms. Hypertrophy of heart
Billings ¹	M. 50	Thromboses of main branches on both	Dyspnea for 8 mo., worse recently. Cough. No edema	Acute pleurisy and chronic fibrous pleurisy. Hypertrophy and dilatation of heart. Thrombosed external jugular vein
Funke ²⁶	M.	Right	Marked cyanosis	Advanced pulmonary tuberculosis Tuberc. involvement of artery wall?
Funke ²⁶	M. 35	Right		General paresis. Gangrene of foot
Smith ²⁷	M. 50	Right and left and extending into right ventricle	Dyspnea and edema	Pulmonary tuberculosis
McPhedran and MacKenzie ²⁸	M. 55	Branches to right lobe	Dyspnea, cough, weakness Edema, large liver	Luetic pneumonia and arteritis
Russell ²⁹	F. 36	Mouth of pulmonary aorta	Dyspnea and cyanosis	Pericarditis—rheumatic
Möller ³⁰	3 cases			Mitral stenosis
Schramm ³¹	F. 44	Aorta and right branch	Dyspnea and cyanosis—5 years	Mitral stenosis
Pick ³²	F. 64	Main stem and branches		Mitral stenosis
Elbogen ³³	M. 44	Main stem		Sclerosis of pulmonary artery
Hoffmann ³⁴	M. 39	Stem and right branch		Sclerosis of pulmonary artery

TABLE I—Continued

Author	Sex Age	Vessel Occluded	Symptoms	Associated Pathology and Remarks
Förster ³⁵	F. 50	Right branch		
Herrmann ³⁶	F. 33	Aorta and both branches	Cough, dyspnea, cyanosis, edema	Postpartum
Löwenstein ³⁷	M. 51	Both branches	Mild cardiac symptoms for 1 year. Recent severe dyspnea and cyanosis	Patent foramen ovale, plugged by emboli
Desclin ³⁸	M. 41	Both branches	Cyanosis, palpitation and fainting for 1½ years Edema, ascites, and cyanosis	Proliferation of intima Thrombosis of right femoral vein. No sclerosis
Desclin ³⁸	F. 62	Main stem	Cyanosis, dyspnea, and edema	Carcinoma of mediastinal lymph nodes
Desclin ³⁸	F. 45	Main branch of right artery	Cyanosis, dyspnea, and edema	Thrombosis of right femoral vein
Desclin ³⁸	F. 49	Main branch, right and left	Dyspnea and weakness	Thrombosis of femoral vein
Desclin ³⁸	F. 65	Main branch of right		Mitral stenosis Thrombosis of left femoral vein
Desclin ³⁸	F. 58	Main branch of right		Carcinoma of esophagus
Desclin ³⁸	F. 56	Both arteries		Carcinoma of breast removed
Desclin ³⁸	M. 45	Both arteries	Dyspnea and cyanosis and fainting. Bronchitis and heart trouble	Thrombosis of both femoral veins Thrombophlebitis 14 years previously
Meldolesi and Dionisi ³⁹	25	Right	Cyanosis, dyspnea and anasarca	Mitral stenosis
Ferraro ⁴⁰	23	Right	Cyanosis and dyspnea	Mitral stenosis
Létulle and Jacquelin ⁴¹	M. 58	Right branch	Passive hyperemia	Syphilis of pulmonary artery

left pulmonary artery was found. A *Streptococcus viridans* grew in post-mortem blood cultures. The second case died 18 hours after a cystostomy, and all branches of the right pulmonary artery were found occluded by organized thrombi. A pyelonephritis and septicemia were also demonstrated. The third case was comatose on admission to the hospital and died four hours later. At necropsy pyelonephrosis and occlusion of the left pulmonary artery by an organizing thrombus were found. A *Streptococcus hemolyticus* grew on postmortem blood cultures.

ETIOLOGY

Thrombosis of the pulmonary artery occurs most frequently as a post-operative or postpartum complication. It has also been reported⁴² in association with cellulitis of the leg, severe burns, typhoid fever, malignant disease of the abdomen, and septicemia. Such cases have not been included in the table. In a study of eight postoperative cases, Glynn⁴³ concluded that a bacterial infection was partially responsible for the thrombus formation in all instances, but the slowing of the blood stream subsequent to their strict confinement to bed was probably a contributing factor. He did not feel that contact of the blood with an abnormal surface was of any significance in the production of the thrombus. Cohen⁴⁴ in an analysis of 35 cases also emphasized the above features but believed that previous damage to the vessel walls was important in certain instances even though infection played the leading part in the etiology. He also pointed out that pulmonary thrombosis occurs more frequently after operations below the level of the diaphragm and that it is much more frequent in adults than in children.

From an analysis of the reports covered by the above table it is seen that pulmonary artery thrombosis was associated with chronic disease of the lungs in 16 cases. These included emphysema, pleural adhesions, bronchiectasis, tuberculosis of either a caseous or fibrotic type, hydrothorax and bronchitis. This group of diseases, together with mitral stenosis, is frequently associated with pulmonary arteriosclerosis.⁴⁵ In some of these cases the arteriosclerotic process was demonstrated, in others no mention was made of the condition of the vessel wall. There were five additional instances in which only arteriosclerosis was found.

In the 62 cases covered by this table, mitral stenosis was present in 12. In this condition there is an increased pressure and a slowing of the blood stream in the pulmonary circuit with sclerotic changes in many instances. There is also the possibility of a low grade intravascular infection, or of an embolus arising from an endocardial vegetation or an auricular thrombus to account for the pulmonary thrombosis. In two cases a patent foramen ovale was found, one of which had a stenosis of the pulmonary orifice. This type of lesion produces changes in the pulmonary circuit similar to those seen in cases of mitral stenosis.

In eight cases there was thrombosis elsewhere in the venous system, in one of which the acute thrombophlebitis had occurred 14 years prior to the pulmonary thrombosis.

Syphilis was present in five cases and will be discussed in more detail later. Other less frequent conditions were cardiac failure without valvular defects (2), carcinoma of the mediastinum (2), chlorosis (1), acute endocarditis (1) and pneumonia (1). In only a few instances was the pulmonary thrombosis considered to be primary.

The immediate cause of the thrombus formation in a given case is difficult to determine and in many instances more than one possible etiological agent is present. The lodging of an embolus in a pulmonary vessel with subsequent thrombus formation is undoubtedly responsible in many instances although it is impossible to determine by microscopic examination whether or not this has been true. Möller³⁰ believes that an embolic origin should be assumed in all cases and this possibility should not be discarded until all possible sources of emboli have been excluded. This is the most logical explanation in those with thrombosis of a peripheral vein, mural thrombus of the right heart or endocardial vegetations.

It would seem that a blood stream infection is the most important etiological factor, particularly when the puerperal and postoperative cases are considered. In the reports analyzed it is difficult to determine the significance of infection. While many of the patients had a febrile course very few bacteriological examinations were made from either blood stream or thrombus.

Arteriosclerotic changes in the vessel walls may be important in certain instances but these changes are frequently present in the pulmonary arteries, whereas thrombus formation is relatively rare, so it is doubtful if arteriosclerosis alone is a significant etiological factor. It is possible that slowing of the blood stream in the pulmonary circulation is of greater significance. This may also be a factor in the production of pulmonary thrombosis in cardiac failure, in comatose states, as well as in postoperative cases with the patient confined strictly to bed.

The rôle of syphilis as an etiological agent is apparently a relatively minor one. Peck⁴⁶ has reviewed the literature on syphilis of the pulmonary artery and accepted only 12 cases as definitely proved. Karsner⁴⁷ reported one case with a productive-cicatricial type of lesion and discussed similar instances in the literature. In his case there was complete obliteration of the left pulmonary artery by the syphilitic lesion rather than by thrombosis. He cited the case of Létulle and Jacquelin⁴¹ which showed a complete occlusion of the right branch by an organized thrombus. In other instances a partially occluding thrombus was present. He emphasized the fact that thrombosis is more common in the pulmonary artery than in the systemic aorta, although the syphilitic involvement of the intima is identical and explains this higher incidence in the pulmonary circuit on the basis of a slower blood flow.

A tuberculous involvement of the vessel wall by direct extension from a pulmonary focus was found in one instance. In another case an inflammatory lesion of the bronchial lymph nodes had apparently extended through the vessel wall and the acute arteritis so produced was apparently responsible for the thrombus formation. Means and Mallory¹⁰ found a calcified mass surrounding the thrombosed pulmonary artery but there was no evidence of constriction or of underlying intimal change. They did not feel that this mass was responsible for the thrombosis.

Chlorosis is given as the etiological factor in only one instance although the possibility of this complication is mentioned in some discussions of the thrombotic tendencies of this disease. Pneumonia is mentioned by several authors as an etiological agent but only one definite example was found. Certain hypothetical agents such as circulating toxins, kinase, histamine and chemical changes in the blood have been mentioned but not demonstrated.

Karsner emphasized the association of occlusion of the pulmonary artery and tuberculosis. In five cases of syphilitic arteritis, even though the occlusion was not always complete, there was a tuberculous involvement of the lung and in one case the tuberculosis seemed to appear while the patient was under observation. He suggested that the circulatory changes contributed to the development of the tuberculous lesion.

It is interesting to note that large infarctions of the lung seldom occur following thrombus formation, which is in striking contrast to the pathologic changes frequently encountered after sudden occlusion by an embolus. This feature was specifically mentioned by many authors. In some cases small infarcted areas were found and in other instances areas of atelectasis. Passive congestion was, however, the most common pulmonary lesion. The absence of gross infarction is explained by the existence of a collateral circulation between the pulmonary and bronchial arteries. Küttner⁴⁸ has demonstrated this anastomosis and in several of the reported cases, especially that of Means and Mallory, the bronchial vessels were markedly dilated. In a few instances, as in Karsner's case of syphilitic arteritis, a collateral circulation had developed through the pleural vessels. The gradual occlusion by a thrombus permits the collateral circulation to develop, whereas this is not possible to any significant extent with a sudden occlusion.

SYMPTOMS

The symptomatology of pulmonary artery thrombosis is extremely variable. In certain cases it develops slowly as a terminal event in a septic patient and no symptoms referable to the thrombosis are produced. In other instances death occurs suddenly with no time for the appearance of symptoms other than the terminal cyanosis and dyspnea. When associated with cardiac failure the manifestations of the thrombosis are masked by those of the primary condition. This is particularly true in mitral stenosis in which a deep cyanosis is already present. In the majority of these cases pulmonary thrombosis is found unexpectedly at necropsy.

We are interested, primarily, in those cases in which the clinical manifestations are referable to the thrombosis alone. The early symptoms are not distinctive. They may consist of an "uneasy feeling," malaise, anorexia, palpitation and fatiguability with some shortness of breath on exertion. Many of these patients give a history of a chronic cough with a sudden intensification of symptoms a few weeks or months prior to death. This may be initiated by an acute upper respiratory tract infection or a localized infection elsewhere in the body and is generally followed by an intermittent febrile course. Cyanosis of a mild degree is common in the early stage and steadily progresses until it becomes one of the most prominent features. Shortness of breath is ordinarily present and in certain instances is the most distressing manifestation. The fact that the vital capacity of the lungs was normal in our case, in spite of the cyanosis and shortness of breath, led us to believe that there was an improper interchange of gases within the lung. Unfortunately the CO_2 content of the alveolar air and blood was not determined. Cough is frequently present, usually non-productive and hacking in character, and may become extremely persistent and distressing. It is to be noted that many cases in the collected reports gave a history of a chronic cough of several years' duration. In a few instances small amounts of bloody sputum have been raised, possibly as a result of small pulmonary infarctions.

Thoracic distress may occur as a dull ache which is not localized or as a sense of oppression or constriction of the chest. In others there are sharp pleural-like pains which may be associated with the slight bloody expectoration mentioned above. Allbutt called attention to the ashen pallor with the facial expression of anxiety such as is commonly seen in coronary artery occlusion.

The pulmonary findings are by no means distinctive and are most frequently those of the associated lesions. The cardiac findings are ordinarily negligible although right ventricular enlargement may ensue in long standing cases. It has been shown experimentally⁴⁹ that occlusion of the pulmonary artery produces little change in the systemic blood pressure or cardiac output until the cross sectional area of the pulmonary artery is reduced 60 per cent. Beyond this point the cardiac output is rapidly diminished and the systemic pressure drops. The fall in blood pressure in the above case is of interest in this regard.

Electrocardiograms showing right axis deviation have been reported. A sharply inverted T-wave in Leads II and III was present in our case and in that reported by Barnes and Yater.⁵ These changes may suggest coronary artery disease but do not show a progressive alteration.

Roentgenological examination has revealed dense hilus areas, and in the case of Boswell and Palmer,²⁴ as well as our own, the shadow of the pulmonary artery was visible but not recognized as such prior to death. Although a definite diagnosis cannot be made on roentgenological examination, a prominent shadow in the region of the pulmonary artery in association

with the above clinical features should direct attention to the possibility of this condition.

Polycythemia was not a significant feature and was present in only one of the collected cases. A mild secondary anemia and a moderate leukocytosis were more common.

Right ventricular failure, as manifested by generalized edema, ascites, and enlargement of the liver, may supervene. In many instances, however, death occurs suddenly, probably because of a sudden obstruction of the remainder of the pulmonary circulation.

CONCLUSIONS

Obliterating thrombosis of the pulmonary artery occasionally occurs as a complication of various cardiac and pulmonary conditions. In most of these cases the thrombosis has not been recognized clinically since the symptoms are masked by those of the primary disease. In a few cases the thrombosis is apparently primary and the symptoms are referable to this alone. While the manifestations are not distinctive, it is believed that in some instances the clinical diagnosis may be possible if the condition is borne in mind. Certain of these cases undoubtedly reach a quiescent stage and it is in that group that its recognition would be most beneficial.

BIBLIOGRAPHY

1. BILLINGS, F. T.: Primary thrombosis of pulmonary artery, *Penn. Med. Jr.*, 1921, xxv, 152.
2. FROTHINGHAM, C.: A case of extensive spontaneous thrombosis of small branches of the pulmonary arteries, *Trans. Assoc. Am. Phys.*, 1927, xlii, 70-72.
3. ROUSLACROIX, and PERRIMOND: Insuffisance du coeur droit chez un bronchitique emphysémateux; thrombose de la branche droite de l'artère pulmonaire; dilatation permanente et insuffisance de ce vaisseau, *Paris méd.*, 1925, lvii, 499-502.
4. LUTEMBACHER: Cited by ROUSLACROIX and PERRIMOND.³
5. BARNES, A. R., and YATER, W. M.: Paroxysmal tachycardia and alternating incomplete right and left bundle-branch block with fibrosis of myocardium; failure of right ventricle due to ancient thrombus in pulmonary arteries; fibromyxoma of left auricle occluding mitral orifice and simulating mitral stenosis, *Med. Clin. N. Am.*, 1929, xii, 1603-1615.
6. ALLBUTT, C.: Thrombosis, pulmonary and elsewhere, *Lancet*, 1924, i, 872-873.
7. DICKINSON, L.: Thrombosis of the pulmonary artery in a case of congenital stenosis of the orifice, *Trans. Path. Soc.*, 1896-1897, xlviii, 57.
8. EIMAN, J.: Thrombosis of pulmonary artery, *Proc. Path. Soc., Phila.*, 1924, xxvii, 52.
9. JUMP, H. D., and BAUMANN, F.: Large thrombus of pulmonary artery with chronic cyanosis and polycythemia, *Penn. Med. Jr.*, 1929, xxxii, 754-756.
10. MEANS, J. H., and MALLORY, T. B.: Total occlusion of right branch of pulmonary artery by organized thrombus, *ANN. INT. MED.*, 1931, v, 417-427.
11. LJUNGDAHL, M.: Gibt es eine chronische Embolisierung der Lungenarterie?, *Deutsch. Arch. f. klin. Med.*, 1928, clx, 1-23.
12. DESCLIN, L., and REGNIER, M.: A propos de la thrombose chronique du tronc et des branches principales de l'artère pulmonaire, *Arch. d. mal du coeur*, 1931, xxiv, 726-740.
13. STADELMANN, E.: Über Thrombose der Pulmonalarterien, *Deutsch. med. Wchnschr.*, 1909, xxxv, 1089-1091.

14. MÖNCKEBERG, J. G.: Über die genuine Arteriosklerose der Lungenarterie, *Deutsch. med. Wchnschr.*, 1907, xxxiii, 1243-1246.
15. RICHTER: Über einen Fall totalen embolischen Verschlusses der Lungenarterie usw., *In Diss.*, Leipzig, 1905; cited by LJUNGDAHL.¹¹
16. NEUMEISTER: Ein Fall von chlorose mit letalem Ausgang infolge von Thrombose der Pulmonalarterie, *In Diss.*, München, 1903; cited by LJUNGDAHL.¹¹
17. WESTPHAL: Über anämische aputride Nekrose grosser Lungenpartien nach Verstopfung von Lungenarterien, *In Diss.*, München, 1907; cited by LJUNGDAHL.¹¹
18. ITTAMEIER: Über einen Fall von Thrombose der rechten A. pulm. und Bildung eines Kolateralkreislaufes in den Lungen, *In Diss.*, Erlangen, 1907; cited by LJUNGDAHL.¹¹
19. TUGENDREICH, J.: Über die Sklerose der Arteria pulmonalis, 1912, E. Ebering, Berlin; cited by LJUNGDAHL.¹¹
20. NEDDERSEN: Über einen Fall von umfangreicher Thrombose der Pulmonalarterie, *In Diss.*, Giessen, 1908; cited by LJUNGDAHL.¹¹
21. BRENNER, O.: Sclerosis of pulmonary artery with thrombosis, *Lancet*, 1931, i, 911-914.
22. GOEDEL, A.: Zur Kenntnis der Hypertrophie des rechten Herzens und schwerer Kreislaufstörung infolge Verödung der Lungenschlagaderperipherie, *Virchow's Arch. f. Path. Anat.*, 1930, cclxxvii, 507-521.
23. HART, C.: Über die Embolie der Lungenarterie, *Deutsch. Arch. f. klin. Med.*, 1905, lxxxiv, 449-458.
24. BOSWELL, C. H., and PALMER, H. D.: Progressive thrombosis of pulmonary artery, *Arch. Int. Med.*, 1931, xlvii, 799-805.
25. SAMEK, E.: Di un caso raro di trombosi primitiva dell'arteria polmonare con successiva embolia retrograda nelle vene renali, *Riforma Med.*, 1928, xlv, 1481-1487.
26. FUNKE, J.: Embolism and thrombosis of the pulmonary artery, *Proc. Path. Soc., Phila.*, 1910, xiii, 249-254.
27. SMITH, C. E., JR.: Thrombosis of the pulmonary artery, with report of a case, *St. Paul Med. Jr.*, 1913, xv, 487-498.
28. MCPHEDRAN, A., and MACKENZIE, J. J.: A case of massive hemorrhagic infarction of the lung due to pulmonary endarteritis and thrombosis, *Trans. Assoc. Am. Phys.*, 1903, xviii, 337-346.
29. RUSSELL: Death from obstruction of the pulmonary artery in the course of pericarditis occurring during the fifth attack of acute rheumatism, *Lancet*, 1872, ii, 707-708.
30. MÖLLER, P.: Studien über embolische und autochthone Thrombose in der Arteria pulmonalis, *Beitr. z. path. Anat. u. z. allg. Path.*, 1922, lxxi, 26-74.
31. SCHRAMM, H. G.: Beitrag zur Aetiologie der Thrombose der Arteria pulmonalis, *Ztschr. f. Kreislaufforsch.*, 1927, xix, 713-726.
32. PICK: Cited by SCHRAMM.³¹
33. ELBOGEN: Cited by SCHRAMM.³¹
34. HOFFMANN: Cited by SCHRAMM.³¹
35. FÖRSTER: Cited by SCHRAMM.³¹
36. HERRMANN, G. R.: Multiple pulmonary infarctions and thromboses, *Med. Clin. N. Am.*, 1923, vi, 1249-1251.
37. LÖWENSTEIN, K.: Über Thromboarteriitis pulmonalis, *Frankf. Ztschr. f. Path.*, 1922, xxvii, 226.
38. DESCLIN, L.: Über chronische Thrombosen des Hauptstammes und der Hauptäste der Arteria pulmonalis, *Frankf. Ztschr. f. Path.*, 1930, xl, 161.
39. MELDOLESI, G., and DIONISI, A.: Tachicardia ventricolare a salve con reperto autoptico di trombosi del ramo destro dell'arteria polmonale, *Bull. e. Atti d. r. Accad. med. di Roma*, 1929, iv, 63-65.
40. FERRARO, P.: Sulla trombosi dell'arteria polmonale, *Riv. Clin. e terap.*, Napoli, 1886, viii, 578.
41. LÉTULLE, M., and JACQUELIN, A.: Anévrismes syphilitiques de l'artère pulmonaire, *Arch. d. mal. du coeur*, 1920, xiii, 385-409.

42. BOX, C. R.: A series of cases in which pulmonary embolism appeared to be due to the displacement of a thrombus in the main trunk of the pulmonary artery, *Brit. Med. Jr.*, 1906, i, 1280; *Trans. Clin. Soc. London*, 1906, xxxix, 189-204.
43. GLYNN, E.: Some observations on fatal cases of pulmonary thrombosis, *Brit. Med. Jr.*, 1910, ii, 1412-1416.
44. COHEN, M. J.: Etiology of pulmonary thrombosis, *Jr. Med. Assoc. S. Africa*, 1927, i, 112-116.
45. MOSCHCOWITZ, E.: Cause of arteriosclerosis, *Am. Jr. Med. Sci.*, 1929, clxxviii, 244-267.
46. PECK, S. M.: Pathologic anatomy of syphilis of pulmonary artery; report of case and review of literature, *Arch. Path. and Lab. Med.*, 1927, iv, 365-379.
47. KARSNER, H. T.: Productive-cicatricial syphilitic disease of pulmonary artery, *Arch. Int. Med.*, 1933, li, 367-386.
48. KÜTTNER: Beitrag zur Kenntnis der Kreislaufsverhältnisse der Säugelhierlunge, *Arch. f. Anat. u. Physiol.*, 1878, lxxiii, 476.
49. GIBBON, J. H., JR., HOPKINSON, M., and CHURCHILL, E. D.: Changes in circulation produced by gradual occlusion of pulmonary artery, *Jr. Clin. Invest.*, 1932, xi, 543-553.

PARENTERAL LIVER THERAPY IN PERNICIOUS ANEMIA: OBSERVATIONS COVERING TWO YEARS OF CONTINUED USE*

By JOSEPH E. CONNERY, M.D., and LEONARD J. GOLDWATER, M.D.,
New York, N. Y.

THE literature on the parenteral use of liver extract in the treatment of pernicious anemia was extensively reviewed by Conner¹ in 1932 and subsequently by others. In the main, except for the recent contributions of Murphy² and of Isaacs,³ the reports which have so far appeared in the literature have to do with the parenteral use of liver extract over relatively short periods of time. In most instances the observations reported cover the effects of this form of treatment during the period of exacerbation, and therefore deal with parenteral liver therapy as an agent in the induction of remissions. It is the purpose of this paper to report the results of the continued parenteral administration of liver extract to a series of patients with pernicious anemia some of whom have been under this form of treatment for as long as two years.

MATERIALS AND METHODS

Some of the patients first came under observation while in a state of relapse sufficiently severe to necessitate hospitalization. Others had been receiving various forms of oral therapy at the return blood clinic, and were changed to parenteral treatment when this study was begun. In the main the patients included in the study were in reduced financial circumstances so that in many instances the problem of obtaining an adequate dietary was solved with great difficulty if at all.

The liver extract used was a commercial solution † of fraction G of Cohn⁴ refined for parenteral administration. During the first six months of the study the extract used was of such concentration that 5 c.c. contained the material derived from 100 gm. of liver. Later the concentration of the preparation was increased so that the same amount of active material was contained in 3 c.c. of solution.⁵ In all instances the injections were made intramuscularly, and in the text the term "parenterally" is used in this sense. The details of the manner of injection have previously been described.⁶ Except those cases which will be specifically designated in the table, all the patients were instructed to take no liver, liver extract, kidney, or other specific anti-anemic substance during the period of study. The patients were, however, instructed to eat liberally of meat (especially red

* Received for publication October 19, 1933.

From the Department of Medicine, University and Bellevue Hospital Medical College, New York University, and the Third (New York University) Medical Division of Bellevue Hospital.

† Prepared by the Lederle Laboratories, New York.

meat), of leafy vegetables, and of fruit. Complete obedience to dietary instructions was impossible in many instances because of poverty. During the period of treatment in the return blood clinic, at regular intervals usually not exceeding three months, an interval history was taken and a complete physical examination made. Blood counts were done frequently, the interval being determined by the status of the patient. The interval between counts rarely exceeded three months. Data were recorded on standardized forms and filed in a unit chart. The personnel of the clinic remained quite constant during the period of the study, so that in the main, observations were made by the same physicians and blood counts done by the same technical staff.

In determining the dose of extract used and the interval between treatments we were guided largely by our previous experience with this form of therapy.⁶ Except in a few instances all patients were given weekly injections of the material from 100 gm. of liver for a period of at least six months. It was felt that in a large group of patients any inadequacy of this treatment would have become apparent in this time in at least some of the patients. It was realized, however, that after a state of remission has been established some patients may show no signs of relapse for a considerable period of time under inadequate therapy, or even with no treatment at all. In general the condition of a patient at the end of the six month period was regarded as satisfactory if the red cell count was about 4.5 million or above, if neurological lesions already present had shown no progression, if no new neurological signs or symptoms had become manifest, if there had been no recurrence of signs or symptoms referable to the gastrointestinal tract, and if the patient continued to enjoy a feeling of general well being.

At the end of the first six month period, the treatment of some of the patients who fulfilled the above criteria was changed so that they were given injections of the material from 100 gm. of liver every second week, instead of every week. A small group, even though their condition was regarded as satisfactory, were continued on weekly injections for a longer period as a further test of the validity of our accepted standards for adequate treatment. Subsequently the treatment of those patients whose status was satisfactory at the end of a second six month period was changed to a three, and in some instances a four week interval. At this point it must be emphasized that the plan just outlined was adopted arbitrarily merely for the purposes of this study, and is not offered of itself as a routine treatment of pernicious anemia. Since our object was to study the effects of prolonged administration of liver extract parenterally, adjuvants to the treatment were purposely omitted.

RESULTS AND DISCUSSION

Red Cells. In the table we have given the month by month red cell counts of all 38 patients included in the study. Where more than one count was done in a month, the first (not necessarily the highest) count of the

TABLE I
MONTHLY BY MONTH COUNTS OF ALL PATIENTS
The sex and age are given with the case number

Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	Date										
F 30	F 50	M 26	F 60	F 73	M 42	F 60	M 02	M 58	F 51	M 50	M 68	M 57	F 68	F 68	F 48	F 55	M 68	F 36	F 61	F 42	F 57	M 71	F 45	F 40	F 02	M 61	M 58	F 60	F 50	M 58	M 73	M 77	M 53	M 58	M 47	M 54	M 31	M 44	1931										
July	Aug.	Sept.	Oct.	Nov.	Dec.	1932	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	1933	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	1934	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.									
3.41	4.58	4.50a	3.17	4.25	2.32	2.44	3.02	3.11	4.39	4.91	3.82	3.07	3.07	3.11	4.40	4.53	4.02	4.53	4.42	4.17	4.55	5.23	5.24	4.39	4.18	4.35	4.89	3.74	3.81	1.43	2.70	3.67	4.47	1.28	4.48	3.18	5.17	3.73	2.12	3.65	4.07	4.10	4.12	4.41	4.60	4.75	5.35	5.21	5.28

* Two week interval begun.

† Four week interval begun.

Three week interval begun.

^a Was taking 1/4 lb. whole liver daily at time parenteral treatment was started, and continued taking whole liver.

Whole liver 1/4 lb. daily added to treatment.

c Iron ammonium citrate 9.0 gm. daily added to treatment.

d Two week interval—injection of material from 200 gm. of liver (6 c.c. of extract).

month was chosen for the table. Inspection of the table at once reveals that with one exception we were not successful in maintaining a count of five million in any of the patients for even a short period of time. However, in a large majority of the patients, the counts were at or above 4.5 million most of the time. If these figures are to be compared with those recently reported by Murphy,² proper evaluation can be made only if the following factors are taken into account: (1) Practically one-half of our patients were in such reduced circumstances that the mere problem of existence was their major concern. (2) Except in three instances (designated in the table) no iron or whole liver was administered. (3) A sufficiently complete list of counts has been given so that all fluctuations are included. (4) Our observations cover a relatively long period of time.

Hemoglobin. Of the 38 patients, 21 were maintained at a hemoglobin level of 13 gm. or more per 100 c.c. of blood. In the remaining 17 the hemoglobin values ranged between 10 and 13 gm. per 100 c.c. of blood. It is possible that the exhibition of iron in large doses might have raised the hemoglobin levels in some of the patients, especially those in the lower bracket. The purpose of this study was to determine the effects of parenteral liver therapy carried over a relatively long period of time. The results of such a study might have been obfuscated had iron been employed.

Clinical Course. In discussing the clinical response to the treatment given, the patients may be divided into two groups: those who had been receiving other forms of therapy and were in a state of remission when parenteral treatment was started, and those who had had no previous therapy. After the red counts in the latter group had reached normal figures, their course differed in no respect from that of the former, so that no separate discussion of the latter is necessary. In no case was there any return of signs or symptoms dependent on the anemia. In no case in which neurological involvement was already present was there any progression nor did any new neurological lesions appear. If no neurological involvement was present when parenteral treatment was started, none appeared during the time the patients remained under treatment. Many patients who were bedridden at the time treatment was started regained the ability of independent locomotion, and some were able to return to useful occupations. Abnormal deep tendon reflexes did not become normal, and impaired vibratory and position sense showed no improvement in any case although in many the functional status was greatly ameliorated. Occasionally there occurred a return of acroparesthesias or glossitis, but these symptoms were always quite mild and of short duration, and bore no relationship to the condition of the blood.

Reactions. In our experience of close to 2000 intramuscular injections of liver extract we have encountered no severe reaction of any type, nor has a single infection resulted. In less than 0.5 per cent mild transitory reactions were noted. These usually took the form of flushing of the face, a feeling of fulness in the head and general body warmth. These symptoms

invariably passed off within a few minutes with no treatment. Pain from the injections was never a serious consideration, and no patient who was offered the alternative of returning to oral therapy (either with whole liver or liver extract) evinced any desire to change.

SUMMARY

1. Thirty-eight patients with pernicious anemia were treated parenterally with liver extract for periods ranging up to two years.
2. Data concerning the red cells and hemoglobin in these patients are given.
3. In a large majority of the patients the red cells remained around 4.5 million during the greater part of the period of treatment.
4. Twenty-one of the patients consistently had hemoglobin values greater than 13 gm. per 100 c.c. of blood. In the remaining 17 the hemoglobin ranged between 10 and 13 gm. per 100 c.c. of blood.
5. Clinically all of the patients remained in a satisfactory condition. A small number had mild transitory symptomatic relapses which bore no relationship to the condition of the blood.
6. No severe reaction to an injection occurred in any case.

BIBLIOGRAPHY

1. CONNER, H. M.: Injection of liver extract in the treatment of pernicious anemia, *Jr. Am. Med. Assoc.*, 1932, xcix, 614-620.
2. MURPHY, W. P.: Maintenance of normal blood in pernicious anemia by means of intramuscular injections of a solution of liver extract, *Am. Jr. Med. Sci.*, 1933, clxxxvi, 271-277.
3. ISAACS, R., STURGES, C. C., GOLDHAMER, S. M., and BETHELL, F. H.: Use of liver extract intravenously in the treatment of pernicious anemia, *Jr. Am. Med. Assoc.*, 1933, c, 629-633.
4. COHN, E. J., MINOT, G. R., FULTON, J. F., ULRICHS, H. F., SARGENT, F. C., WEARE, J. H., and MURPHY, W. P.: The nature of the material in liver effective in pernicious anemia, *Jr. Biol. Chem.*, 1927, lxxiv, p. lxxix-lxxii.
5. Solution liver extract parenteral, N. N. R., made by the Lederle Laboratories, Inc., New York.
6. CONNERY, J. E., and GOLDWATER, L. J.: Parenteral use of liver extract in treatment of pernicious anemia, *Jr. Am. Med. Assoc.*, 1932, xcvi, 1060-1067.

MUCIN IN THE TREATMENT OF PEPTIC ULCER ASSOCIATED WITH RENAL AND HEPATIC DISEASE*

By ANDREW B. RIVERS, M.D., F.A.C.P., *Rochester*, and FRANCES R.
VANZANT, M.D., *Minneapolis, Minnesota*

THE usefulness of mucin in the treatment of peptic ulcer has been widely discussed for several years. The efficacy of this substance as a therapeutic agent is assumed to depend largely on its diluent and neutralizing effect on gastric acidity, and on its ability to protect gastrointestinal tissues locally against the proteolytic action of the acid gastric chyme. That it has some virtue in the treatment of peptic ulcer is strongly suggested by the brilliant results obtained by Fogelson,¹ Atkinson,² Brown³ and other investigators. Our⁴ experience with mucin has not been equally successful; nevertheless the striking results occasionally obtainable even in intractable⁶ cases of ulcer have induced us to continue its use.

In certain types of ulcer especially beneficial results from the use of mucin are obtained. We have been of the opinion that pathologic processes which need only a favorable type of local gastroduodenal chemism to induce quiescence should the more easily and quickly heal when mucin is used in their treatment. Acute and subacute ulcers, areal inflammatory lesions, or other ulcers which may have resulted from trauma to a single tissue, together with eroding gastric chemism, should respond favorably to any treatment which renders less innocuous the aggression of such a gastric chyme. It is probable that mucin accomplishes this. In those cases, however, in which systemic, and especially neurogenic, factors contribute largely to the cause and course of the ulcer syndrome, it is doubtful whether mucin can be expected to accomplish anything more than the production of transient benefit.

When we began using mucin,⁵ we noted that certain batches of this substance contained an objectionable amount of a secretagogue which when assayed showed the biologic characteristics of histamine. At present the product which has been furnished us contains much less of this secretagogue, although at times some of the samples still seem to contain an objectionable substance which accentuates gastric secretions.

One of the desirable accomplishments in the treatment of peptic ulcer, whether by surgical or medical means, seems to be reduction of gastric acidity. We have attempted to substitute mucin for alkalies in order to accomplish this, because the use of alkalies occasionally seemed to produce an increased secretory activity of the fundic glands. It is then difficult to control or materially to reduce acidity, and often the immoderate increase of

* Submitted for publication May 22, 1933.

From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota, and the University Hospital, Minneapolis, Minnesota.

the amount of alkalies used to accomplish neutralization will result in symptoms of toxemia.⁶ Accompanying this, there will be an elevation of the concentration of urea in the blood and an increase of the carbon dioxide combining power of the blood plasma. This alkalosis is prone to complicate the treatment of peptic ulcer in the presence of associated hepatic or renal disease. It was thought that the substitution of mucin for alkalies in such cases would accomplish the desired lowering of gastric acidity without exposing the patients to the complication of alkalosis. We were, therefore, disappointed to find that frequently in precisely the type of case in which alkalosis is likely to develop, and particularly in cases in which the hepatic or renal tissues are seriously injured, the use of mucin may be productive of decidedly untoward results. The following two reports of cases are illustrative of some complicating features that may develop following the use of mucin in cases in which renal disease is associated.

CASE I

A man, aged 46 years, first came to The Mayo Clinic in 1929, because of abdominal pain which had been present for three years. A clinical and roentgenologic diagnosis of duodenal ulcer, with slight gastric retention, was made at that time. He was given medical treatment. He returned to the clinic two years later because of persistence of the duodenal ulcer and the recent development of urinary symptoms. A diagnosis of bilateral pyelonephritis with multiple cortical abscess was made. A few months later posterior gastroenterostomy was performed to relieve obstruction due to a subacute perforating duodenal ulcer. Following this, there was relief of the dyspepsia for one year, when there was a recurrence of distress occurring across the lower part of the abdomen. A diagnosis of gastrojejunal ulcer was made. The infection in the urinary tract had persisted in spite of much treatment, although the lesion did not seem to have progressed. The concentration of urea was slightly elevated, ranging from 48 to 54 mg. in each 100 c.c. of blood, which was the same as it had been a year before. An ambulatory type of ulcer diet was prescribed with 60 gm. of mucin three times a day and a small amount of alkali. One week later it was observed that the concentration of urea was 72 mg. in each 100 c.c. of blood. The use of alkali was then discontinued. Three days later the value of urea was 62 mg. and the carbon dioxide combining power of the plasma was 28 per cent by volume. It was found that discontinuance of the mucin would allow the value for blood urea to fall to its previous level, the carbon dioxide combining power to rise to normal. The administration of mucin for a few days would cause the concentration of urea to rise to 70 mg. in each 100 c.c. of blood, the carbon dioxide power to fall as low as 28 per cent by volume, and the dyspepsia to be relieved.

CASE II

A man, aged 70 years, came to the clinic because of indigestion dating back approximately three years. The indigestion had all of the characteristics of peptic ulcer. A year prior to his admission gastrointestinal hemorrhage had occurred, manifested by hematemesis, melena, syncope, and anemia. The patient also had definite evidence of coronary sclerosis, and during the course of his examination evidence of associated nephritis developed. The estimation of gastric acidity, titrated against sodium hydroxide, showed values of 98 for total and 57 for free hydrochloric acid. Fluoroscopic examination revealed a definite duodenal deformity which was assumed to be due to a peptic ulcer. The value for urea was 84 mg. in each 100 c.c. of blood;

creatinine, 2.10 mg. Examination of urine disclosed albumin, hyaline casts, and occasional erythrocytes. The carbon dioxide combining power of the plasma was within normal limits. The intake of protein was restricted to 50 gm. The patient was frequently given small amounts of milk. He responded well to a nonsurgical regimen for ulcer, which included the use of 60 grains (4 gm.) of alkali daily. The concentration of urea in the blood promptly dropped to 52 mg. After several weeks he was dismissed from observation, and advised to continue with a restricted diet, the ingestion of milk between meals, and a limited amount of alkali.

The patient continued well for four months. Then recurring gastric difficulties developed and he returned to the clinic for further examination. It was assumed that a reactivation of the duodenal ulcer had occurred. The concentration of urea was found to be 40 mg., and of creatinine 1.5 mg. in each 100 c.c. of blood. He was again hospitalized, put on a restricted protein diet with small amounts of milk at frequent intervals between meals, sedatives, and 80 gm. of mucin daily. Alkali was not used at this time. Although there was prompt improvement in the gastrointestinal symptoms, the urea in the blood soon began to increase, ranging from 46 to 72 mg. The carbon dioxide combining power of the plasma fluctuated between 64 and 48 per cent by volume. After several days slight indigestion again developed, and it was decided to supplement the mucin with 80 grains (5.2 gm.) of alkali. Within two days the concentration of urea became elevated to 82, and there was a prompt shift of the carbon dioxide combining power of the plasma to 92. It was then decided to decrease considerably the amount of the alkalies as well as of mucin, and promptly there was a drop in the carbon dioxide combining power of the plasma to 58, and within a few days the concentration of urea fell to 52.

COMMENT

Similar elevation of the value for urea following the use of mucin has been noted in several other cases with associated peptic ulcer and renal disease. In such cases there is usually parallelism between the height of the value for urea and the amount of mucin used. On discontinuing administration of mucin the value for urea would promptly drop to its basic level. In several instances there was a definite drop of carbon dioxide combining power of the plasma toward the side of acidosis. There would be prompt restoration of the carbon dioxide combining power to normal when administration of mucin was stopped. One hundred grams of mucin include approximately the equivalent of 70 gm. of protein. This, when added to proteins already included in the diet of patients with nephritis, might well be the causative factor in producing elevation of the value for blood urea. Whether such elevation is due to the protein content of mucin alone is still not decided. Adding a corresponding amount of ordinary food protein to the diet of one of these patients resulted in some retention of nitrogen, but to a slightly smaller degree. It is possible, therefore, that some specific toxic derivative of protein is still contained in the mucin.

Similar untoward effects were noted in some cases of associated hepatic disease and peptic ulcer. Such patients seem to have an increased liability to the development of alkalosis when they are given enough alkali to neutralize their gastric acids. It was therefore thought that mucin might be substituted for alkalies and thus prevent the establishment of alkalosis. Definite signs of toxemia, however, resulted promptly in some of these cases

following the use of mucin. We are still uncertain regarding the exact nature of the substances contained in mucin which were responsible for these symptoms. It is, of course, possible that the protein factor alone is responsible.

SUMMARY

Ordinarily, if patients have uncomplicated peptic ulcer the use of 100 gm. of mucin daily does not cause changes in the value for blood urea. The use of mucin, however, if patients have ulcer and associated advanced hepatic or renal disease, should be carried on with caution, because untoward symptoms may develop during the course of the treatment. It has been our custom when such complications exist to use smaller amounts of alkalies and mucin in order to accomplish reduction of acidity. Apparently, such patients get along very well on this modified type of treatment.

The specific cause of untoward effects produced in certain cases with marked hepatic or renal disease has not been determined, although it is possible that the protein factor alone or some protein derivative is the cause of these untoward effects.

REFERENCES

1. FOGELSON, S. J.: Treatment of peptic ulcer with gastric mucin; preliminary report, Jr. Am. Med. Assoc., 1931, xcvi, 673-675.
2. ATKINSON, A. J.: Gastric mucin in the treatment of peptic ulcer, Jr. Am. Med. Assoc., 1932, xcvi, 1153-1156.
3. BROWN, C. F. G., CROMER, S. P., JENKINSON, E. L., and GILBERT, N. C.: Mucin therapy for peptic ulcer: preliminary report of objective results on patients with intractable ulcer, Jr. Am. Med. Assoc., 1932, xcix, 98-100.
4. FOGELSON, S. J.: Clinical experiences in the treatment of peptic ulcer with gastric mucin, Illinois Med. Jr., 1932, lxii, 516-520.
5. RIVERS, A. B., VANZANT, F. R., and ESSEX, H. E.: Dangers of using impure mucin in the treatment of peptic ulcer, Jr. Am. Med. Assoc., 1932, xcvi, 1156.
6. HARDT, L. L., and RIVERS, A. B.: Toxic manifestations following alkaline treatment of peptic ulcer, Arch. Int. Med., 1923, xxxi, 171-180.

THE REDUNDANT DUODENUM: CLINICAL SIGNIFICANCE *

By THEODORE H. MORRISON, M.D., F.A.C.P., and MAURICE FELDMAN, M.D., *Baltimore, Maryland*

ALTHOUGH anomalies of the duodenum are occasionally observed in the routine roentgenological examination of the gastrointestinal tract, little attention has been paid to them clinically. With the development of roentgenologic technic in gastroenterology, more of these conditions are being discovered and as a consequence their clinical significance is becoming recognized. Abnormalities of the duodenum are frequently overlooked during an ordinary barium meal study principally on account of the fact that the examiner concentrates his attention on the first part of the duodenum or cap. It is quite probable that, were the entire duodenum studied with the same meticulous care, many more instances of duodenal abnormalities would be discovered. From our study we are convinced that anomalies of the duodenum are far more common than a survey of the literature would indicate. Furthermore, we believe that with the increased attention that has recently been directed to this part of the intestine, together with the improvement in roentgen interpretation, many more cases will be discovered and their full significance understood. The roentgenological aspect of this anomaly has recently been described by one of us,¹ and in the present communication we especially direct attention to the clinical importance of this condition.

In order more fully to comprehend the significance of these malformations, it might be well to review briefly certain salient anatomical features associated with the normal duodenum. This portion of the intestine is about 10 inches in length and has a definite configuration either in the shape of an incomplete circle or in the form of a "C." Under abnormal conditions, however, it may assume bizarre forms, varying from U-shaped to V-shaped and to other obvious distortions. The first portion of the duodenum is the most mobile; the remaining portions are practically fixed and bound down by the adjacent viscera and partially by peritoneum. Although the first portion of the duodenum is the most movable it is, however, somewhat fixed by the hepato-duodenal ligament. This represents the free margin of the lesser omentum. A fold of the hepato-duodenal ligament extends down from the posterior surface of the gall-bladder to the descending portion of the duodenum. This fold is known as the hepato-colic ligament, hepato-duodeno-colic ligament, cysto-colic ligament or fold, or cysto-epiploic ligament. It is evident, therefore, that the hepato-duodenal and

* Read at the meeting of the American Gastro-Enterological Association in Washington, D. C., May 10, 1933.

From the Gastro-Enterological Clinic of the Department of Medicine, University of Maryland, Baltimore, Md.

hepato-colic ligaments play an important rôle in the fixation of the superior segment of the duodenum.

In this study we desire especially to call attention to redundancy of the superior portion of the duodenum. The several ligaments originating in the fold referred to above are largely responsible for the maintenance of the looping observed in the "redundant duodenum," a term by which we have designated the condition under discussion. It is an interesting anomaly which has heretofore frequently been overlooked.

In the course of our routine roentgenological studies of the gastrointestinal tract, we have occasionally encountered an elongation or lengthening of the superior portion of the duodenum and in all of these, a ptosis of the superior segment was noted which resulted in an anomalous loop. As a result a puddling and retardation of the contrast meal was produced and the final picture is that of a water trap in which the passage of the opaque meal appears to be delayed. Careful observation discloses definite fixation of the superior angle of the duodenum with displacement posteriorly from its normal position. In addition, the superior segment of the duodenum is likewise fixed at its anterior portion, namely at the junction of the first part or cap with the second part of the duodenum. The unusual lengthening of the superior segment results in a sagging, ptosis and looping, producing the characteristic picture of the redundant duodenum. The two fixed areas in the superior portion are well illustrated in figures 1 (B) and 2. This elongated segment of the superior duodenum varies in length from five to ten centimeters. Several types of deformities have been observed, such as the U-shaped, V-shaped, double looping and the serpentine forms. Occasionally, only a slight sagging of the elongated segment is noted. A typical illustration of a redundant duodenum is shown in figures 1 (B) and 2.

Under normal conditions the roentgen-ray examination of the duodenum presents the first portion or bulb surmounted upon the pyloric outlet, which is directed upward, slightly to the right and frequently somewhat posteriorly. This is commonly known as the superior portion and is usually not more than five centimeters in length. At the apex of the bulb or duodenal cap, the second portion is observed to form an angle with the first part and then descends downward, to the right and posteriorly. Normally, no transverse elongation of this section of the duodenum is observed. The angulation of the superior portion is easily recognized and is more or less fixed by the hepato-duodenal ligament. From this angulation the descending portion seems to take a sudden drop. However, in those instances in which the redundant duodenum is present, this picture appears quite altered. There is present a marked elongation or lengthening of the superior segment. The duodenal cap is not affected and seems to be normal in position and size. In some instances at first glance the extra loop appears as an integral part of the cap which produces the impression of an enlarged cap or diver-

ticulum. This is due to the coalescing of the extra loop with the cap shadow. However, upon manipulation no connection can be demonstrated.

The redundant duodenum with which we are here concerned usually involves the superior segment although occasionally the entire duodenum may be included. It has been variously described as a ptosis, festooning, idiopathic elongation, M-deformity or an extra looping, terms which can not be considered entirely satisfactory. It seems apparent that since the duodenum is of greater length than normal, the term redundant duodenum or dolichoduodenum should be adopted as being more accurate as well as

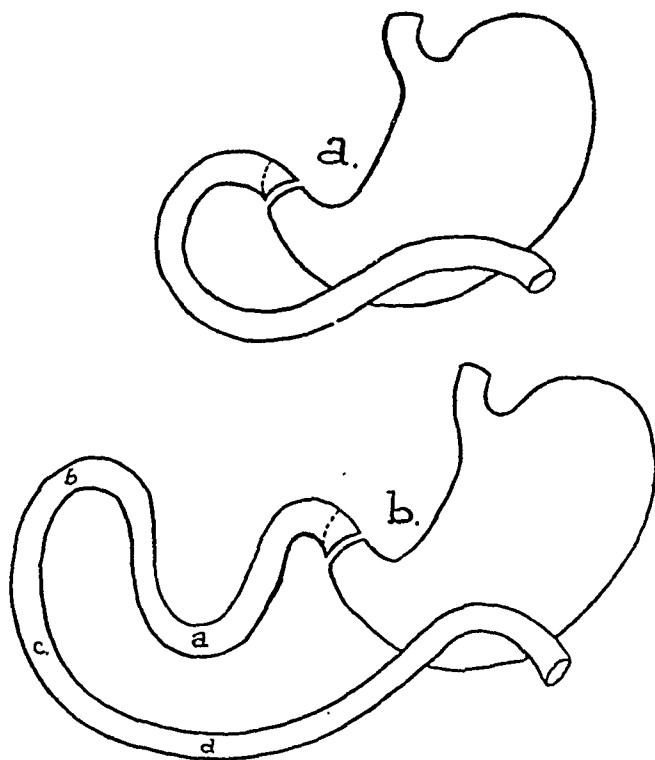


FIG. 1. *A* illustrates a tracing of the normal outline and curve of the duodenum. *B* is a tracing of a redundant duodenum, with looping at *A* shown.

descriptive. This would correspond more definitely with the nomenclature which is applied to similar conditions such as for example the redundant colon.

The literature contains but few references to this anomaly. Castrovano² alludes to it in describing certain malformations of the duodenum and Duval, Roux and Béclère³ likewise refer to it. Dall'Acqua⁴ describes seven instances of mobile duodenum. He points out that in the type in which the partial mobility occurs the roentgen-ray examination revealed a double festoon or complete scroll above the fixed portion of the descending part. Kellogg,⁵ Quénu and Jacquelin,⁶ Brdiczka⁷ and Tartagli⁸ point to the occasional occurrence of this deformity. The anomaly, it can be seen,

is of considerable interest and its recognition is of some importance inasmuch as it is frequently associated with disturbances of motility of the duodenum as well as with ulceration in this area. The diminished motility with its consequent stasis, the retardation and lagging revealed in the contrast meal, all point to the important rôle which such changes may play in the production of syndromes otherwise difficult to understand. These

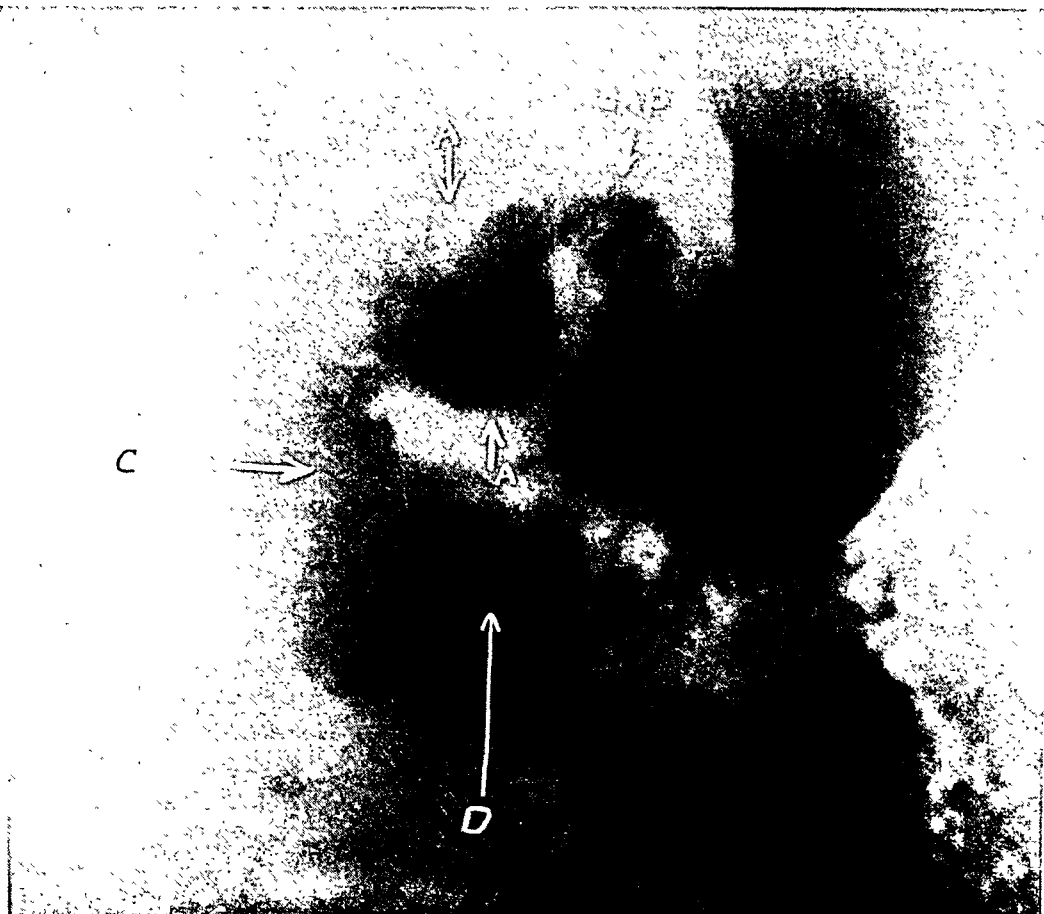


FIG. 2. Roentgenogram illustrating the lengthened superior segment of the duodenum. The duodenal cap is poorly filled on the film, but it filled well under the fluoroscope. It was markedly irritable and suggested a duodenitis. *A*—extra loop. *B*—point of fixation. *C*—descending duodenum. *D*—transverse segment of duodenum.

cases therefore merit careful study, and their early recognition is important so that effective treatment may be instituted in order to prevent the production of secondary complications.

As a result of our interest in duodenal anomalies, we have discovered 12 cases, in a series of about 500 routine gastrointestinal studies, all of which present definite elongation of the superior portion of the duodenum with sagging and looping of this segment. The ages of the patients, of which nine were male and three female, ranged between 25 and 57 years.

Important Findings in Twelve Cases of Redundant Duodenum

Number	Name	Sex	Age	Acidity		Loss of weight	Appetite	Pain	Nausea	Vomiting	Migraine attacks	Constipation	Complications			
													Ulceration		Duodenal stasis	Irritable duodenum and duodenitis
													Duodenal	Gastric		
1	R.I.	M	33	70-90		+	+	0	+	0	0	0	0	0	+	+
2	B.M.	M	53	55-71		+	+	+	+	+	+	+	+	0	+	+
3	C.E.	F	31	24-42		+	+	0	0	0	+	0	+	+	+	+
4	D.B.	F	27	34-50		+	+	0	0	+	+	+	+	+	+	+
5	B.C.	M	40	0-28		+	+	+	+	+	+	+	0	0	+	+
6	B.J.	M	57	48-66		+	+	+	+	0	0	+	0	0	+	+
7	S.H.	M	39	52-65		+	0	+	+	+	+	+	+	0	+	+
8	P.A.	M	25	50-78		+	+	0	0	0	0	0	+	0	+	+
9	G.F.	M	46	54-73		+	+	0	0	0	0	+	0	+	+	+
10	W.H.	M	26	27-38		+	0	0	0	+	+	+	0	0	+	+
11	R.W.	M	35	68-104		+	+	+	+	0	0	+	0	0	+	+
12	R.E.	F	45	22-54		+	+	0	0	0	0	+	0	0	+	+

The symptoms are by no means characteristic. It is probable that many of these conditions exist without producing any symptoms whatever and on the other hand many symptoms no doubt arise at times as a result of an associated complication. The patient usually complains mainly of loss of appetite, nausea, discomfort in the epigastrium, vomiting, headaches and migraine attacks often of a periodic type. Abdominal pain is rarely severe and when it occurs is usually mild in character. In many instances so-called bilious attacks occur which have extended over a period of many years, often since childhood. They are frequently preceded by constipation. The constipation is replaced occasionally by intermittent diarrhea. Duodenal stasis is usually present and may account for many of the symptoms. When the attacks are frequent, loss of weight and strength supervene and in certain individuals neurasthenic symptoms become a prominent part of the symptomatology. On the other hand, remissions may occur with a disappearance of symptoms and for varying intervals the patient may enjoy comparatively good health. As a rule gastric retention does not occur in this affection and in none of our cases was gastric motility markedly disturbed. Attacks of nausea occurred in nine of our cases, vomiting in five, migraine attacks in five, constipation in nine, intermittent diarrhea in three. Pain, mild in type and not related to the intake of food, occurred in only five instances. Occasionally the liver may enlarge during an attack and tenderness may then be observed under the right costal arch. The gastric secretion is variable. In our series hyperchlorhydria occurred in seven cases, normal acidity in four and achylia in one.

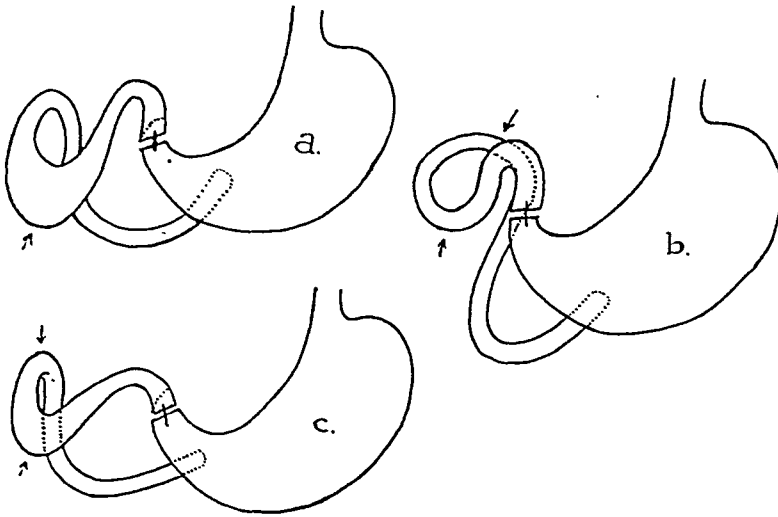


FIG. 3. Tracings of redundant duodenum *A, B, C*.

Diagrams of fluoroscopic views of the more common forms of redundancy observed in the superior portion of the duodenum. These show the posterior direction of the descending duodenum.

Duodenal dilatation and stasis is noted in the loop in *A*. *B* shows a posterior and inward displacement of the descending segment. Acute angulation with slight duodenal stasis is shown in *C*.

In order to clarify the clinical picture which may accompany redundant duodenum the following case history is presented.

CASE HISTORY

A. P., male, aged 25 years, complained of indigestion, of 10 years' duration. The principal symptoms were nausea, regurgitation, dizziness, constipation, lack of appetite, fullness and distention after meals and discomfort in the upper right quadrant. The attacks of discomfort were at first experienced only periodically but recently they have become almost continuous. He has been living on a restricted diet and has lost 10 pounds in the past few months. On physical examination his chest was normal. The abdomen was negative with the exception of an area of distinct tenderness in the epigastrium. The test meal showed a total acidity of 78, and free HCl 50. The roentgen-ray examination was as follows: The position of the stomach is normal. There are no filling defects present. The pylorus is spastic; the duodenal cap is markedly irritable; no definite defect is observed. The superior portion of the duodenum presents a marked elongation, with a loop deformity producing a water-trap effect and resulting in a moderate degree of stasis. The colon is normal in position and incompletely filled. The diagnosis of redundant duodenum was made. The roentgenogram of this case is shown in figure 2.

From the foregoing it is evident that the redundant duodenum should be considered as a definite roentgenological entity which may be recognized by the presence of the unusual lengthening of the duodenum. Clinically, it may be significant that in our small series of cases with this anomaly peptic ulcer was frequently found and gall-bladder infections rarely so. Another interesting observation noted in this group of cases was the presence of duodenitis or marked irritation of the duodenum in those instances in which

ulceration was not present. Even when the clinical history was suggestive of ulcer, the roentgenological findings were not always corroborative. In some of these instances the picture observed was that of duodenitis or irritability of the duodenum. Duodenal retardation with stasis was observed in every instance. In our series the roentgen examination presented evidence of ulceration in five cases, duodenal in three, pyloric in one, and gastric in one. Duodenitis and irritable duodenum, which are considered by many to be precursors of actual ulcer, were found in the remaining cases. This association is not merely coincidental. It may be interpreted in the light of our present theories regarding the etiology of ulcer, as a direct effect of the redundant condition of the duodenum with its resultant stasis and consequent local injury to the mucous membrane.

In this study it seemed important to determine whether the relative positions of the stomach and colon bore any definite relationship to that of the redundant duodenum. In six instances the position of the stomach and colon was observed to be normal; in one a slight ptosis was noted; in two a moderate ptosis; in only three was a marked ptosis of the stomach and colon observed. It seems, from these findings, that the position of the stomach and colon bears no special relationship to the redundancy of the duodenum.

The diagnosis is not as a rule possible from the history and physical findings alone but must be based largely upon a roentgen-ray investigation. Though the condition is best recognized under the fluoroscope, this anomaly may also be recorded on the films, when the patient is placed in the proper position. The fluoroscopic examination is usually most satisfactorily made with the patient in the upright posture, viewed antero-posteriorly, obliquely and laterally. The duodenum is best observed in the upright posture when viewed under the fluoroscopic screen. The oblique view seems to bring the entire duodenum on the screen and is the ideal position in which to visualize this condition since the duodenum in these cases is directed well posteriorly and the redundancy is often not clearly visible in the antero-posterior position. Examination should also be made routinely in the prone position. Occasionally the looping of the redundant duodenum disappears in the recumbent posture. When this occurs the serpentine appearance of the lengthened segment is observed. During the fluoroscopic examination the entire duodenum can be manipulated and the redundant segment, which may otherwise escape visualization, be brought into view. Most frequently one observes a puddling in a loop hanging from the mid-superior portion of the duodenum, between the cap and the descending sections. As has already been stated this has the appearance of a water-trap, which definitely retards the outflow of the contrast meal and which at once gives a clue as to the possibility of the presence of this abnormality. On manipulation this puddling entirely disappears, only to return with the next spurt of the opaque meal through the duodenum. In some instances

sharp angulation exists, which may cause delay in the expulsion of the contrast meal through the duodenum.

In studying this anomaly by careful roentgenological methods in the attempt to find an explanation for the double fixation of the superior duodenum the impression was gained that this may not be secondary to acquired adhesions but more probably is of congenital origin. The fixation may be due to the presence of peritoneal bands, represented by the hepato-duodenal and the hepato-colic ligaments; and the occurrence of a redundant superior duodenum is best explained upon the basis of a congenital malformation, in which the duodenum is lengthened, so that it cannot fit into the space allotted to it. The anomaly therefore seems to be dependent not only upon the abnormal fixation of the superior portion of the duodenum but also upon its unusual length.

In considering the diagnosis it should be recognized that the redundant duodenum occurs sufficiently frequently to be borne in mind in doubtful conditions involving the right upper abdomen. It is always important, however, that repeated roentgen-ray examinations be made, in order to be certain that the redundancy is permanent. These were made in the cases of our series. Since headaches associated with nausea and vomiting are often present, it is important in all obscure forms of migraine to make thorough roentgenological studies of the duodenum in order to determine any abnormality of duodenal function. In some instances, the symptoms may be attributed to gall-bladder disease, duodenal stasis, ulcer or even neurasthenia. Roentgenologically, the redundant loop may be simulated by a number of conditions such as accessory pockets of a duodenal ulcer, inverted duodenum, dilated bulb, duodenal diverticula, filled ampulla and by various other duodenal deformities resulting from adhesions in the upper right portion of the abdomen.

In the treatment of this condition conservative medical management is usually sufficient to bring about symptomatic relief, especially since in the majority of these cases periods of well being are quite characteristic. Diet plays an important rôle in the treatment. It should be of the bland type and of a high caloric content. Occasionally, it may be advisable to suggest a rest in bed of from four to six weeks, during which time general up-building measures, elevation of the foot of the bed, and treatment directed toward overcoming the associated conditions may be undertaken. This plan is especially indicated in those instances associated with marked enteroposis, ulcer and the more severe grades of duodenal stasis. Transduodenal lavage with magnesium sulphate or Ringer's solution is usually very beneficial. When the symptoms are unusually severe or when adequate medical treatment no longer affords relief, surgical intervention is indicated, the most satisfactory procedure in most instances being duodeno-duodenostomy, duodeno-jejunostomy or gastro-jejunostomy. At the time of the operation a thorough exploration of the abdominal organs should be made and, depending on the patient's condition, any associated pathological lesion

that may be discovered should, if possible, be corrected. For example, if the gall-bladder is found to be diseased it should be removed, or if an ulcer is detected it should be treated according to the usual surgical procedure.

Of the 12 cases in our series, six were markedly benefited by means of the usual medical management, four were somewhat improved and in two no relief was obtained. Operation was not performed in any of our cases.

SUMMARY

Anomalies of the duodenum are far more common than is indicated by a survey of the literature. Of these the redundant duodenum is of considerable interest since it is frequently associated with disturbances of motility of the duodenum as well as with ulceration.

Clinically, there is no characteristic symptomatology, the picture being that of the associated lesion. Many instances undoubtedly occur without presenting any symptoms whatever.

The diagnosis is not as a rule possible from the history and physical findings alone but must be based almost entirely upon the roentgen-ray investigation.

Finally, these cases deserve careful study since their early recognition and effective treatment may prevent the occurrence of secondary complications.

REFERENCES

1. FELDMAN, M.: Redundant duodenum, *Am. Jr. Med. Sci.*, 1933, clxxxvi, 198-202.
2. CASTRONOVO, E.: Intorno ad alcune malformazioni congenite del duodeno considerate nei loro rapporti con la clinica, *Radiol. med.*, 1927, xiv, 1077-1099.
3. DUVAL, P., ROUX, J. C., and BÉCLÈRE, H.: The duodenum; medical, radiologic and surgical studies, 1928, C. V. Mosby Co., St. Louis, page 20.
4. DALL'ACQUA, V.: Gli aspetti radiologici del duodeno mobile, *Radiol. med.*, 1930, xvii, 781-802.
5. KELLOGG, E. L.: Abnormalities in the shape and position of the duodenum, *Am. Jr. Surg.*, 1931, xii, 462-465.
6. QUÉNU, J., and JACQUELIN, C.: Des déformations sus-mésocoliques en "M" du duodénum et de leurs stades évolutifs, 7 observations, *Arch. d. mal. de l'app. digestif*, 1932, xxii, 601-624.
7. BRDIZKA, J. C.: Abnorme Schleifenform der pars superior Duodeni und ihre differentialdiagnostische Bedeutung, *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1931, xliii, 222-225.
8. TARTAGLI, D.: La morfologia duodenale sotto il rispetto anatomoradiologico, *Radiol. med.*, 1931, xviii, 289-308.

THE HEREDITARY AND FAMILIAL FACTOR IN HYPOCHROMIC ANEMIA WITH ACHLORHYDRIA *

By WILLIAM H. BARROW, M.D., F.A.C.P., *San Diego, California*

HYPOCHROMIC ANEMIA with achlorhydria, or achlorhydric anemia, was first described by Faber ¹ in 1913. During the past few years there have been much discussion and speculation in the literature in regard to this blood dyscrasia which has now been established as an easily recognizable clinical syndrome. The characteristic picture is that of an idiopathic secondary anemia occurring usually in women of middle age, the blood showing a low color index and red blood cells of small corpuscular diameters. Gastric analysis reveals an absolute achlorhydria, and there is occasionally a splenomegaly.

The familial incidence of this disease has not been discussed at length in the literature, although references are made to the occurrence of the disease in families in which pernicious anemia is also found. Wits ² states that the occurrence of secondary anemia in female members of the family in which pernicious anemia also exists is not well known but does definitely exist, and cites cases reported in the literature. Among others he mentions a female patient, her mother and her aunt, all of whom were cases of secondary anemia. Special inquiry for evidence of familial anemia was not made in his series, but in three instances a family history of anemia was given. The mother of one patient had pernicious anemia, a sister of another had an undetermined anemia, and in another patient's family there were several cases of pernicious anemia. This last patient herself developed pernicious anemia after having had the achromic form. Wits notes that in the family histories the anemic males are apt to have a primary anemia and the females a secondary type. He suggests that the achromic anemias seem to be the equal in the female of "pernicious anemia in the male. In his series there was only one male with this type of anemia.

In discussing achylia gastrica and achlorhydria Friedenwald and Morrison, ³ and Hurst, ⁴ mention the occurrence of this condition in several members of the same family. Hurst states that there is a familial or hereditary type of achlorhydria, which occurs, however, in not more than 2 per cent of all cases. Seventeen families are reported, with achylia present in two or more members of each family, none of whom, however, showed any evidence of anemia. He mentions other cases reported by several authors among which are instances of Addisonian anemia and simple achlorhydric anemia occurring in the same family. He believes that anemia of either form is secondary to the achylia, 'whether this achylia be familial or due

* Presented in part at the joint meeting of the Pathology and Bacteriology and General Medicine Sections of the California Medical Association at the sixty-second annual session, Del Monte, April 24 to 27, 1933. Received for publication November 1, 1933.

to some other cause. Faber¹ advanced the theory that the achylia results in a production of bacterial toxins in the intestinal tract with a resulting hemolysis. Waugh⁵ ventures the opinion that the anemia may be due to a deficiency in the gastric secretion with the absence of some substance essential to the maintenance of normal hematopoiesis.

McCann and Dye⁶ suggest the possibility of a familial incidence of the disease, mentioning that one patient reported by them had a sister who presented the same symptoms of anemia, general weakness and arthritis. Heath⁷ reports two cases of hypochromic anemia in women in their forties, neither one of whom gave any family history of anemia. With reference to the familial incidence of the disease he agrees that hypochromic anemia may be found in families in which other members have pernicious anemia, and he accepts the theory presented by Faber, Waugh and Witts that the anemia is gastrointestinal in origin. He advances the idea that there is possibly some substance present in normal gastric juice and absent in achlorhydria which aids in the absorption of iron.

Castle, Heath and Strauss,⁸ and Morris and his co-workers,⁹ have reported experimental and clinical evidence of a specific hematopoietic hormone in the normal gastric juice which is lacking in patients with primary anemia. They state, however, that the presence of this hormone is not dependent on the presence of hydrochloric acid in the juice, it being found in some cases of uncomplicated achlorhydria and in achlorhydric hypochromic anemia.

In a recent monograph on idiopathic hypochromic anemia Wintrobe and Beebe,¹⁰ in a discussion of the familial incidence of the disease, review the cases in the literature with a familial history of anemia. They point out the not uncommon association of pernicious anemia and hypochromic anemia in the same family, and report a family history of anemia in two out of 22 of their own cases. The father of one patient had had pernicious anemia, and another patient had a cousin who had an achlorhydric form of anemia that was probably of the hypochromic achlorhydric type. Among all the cases referred to in this monograph the greatest number of cases occurring in the same generation is two, although there are two families reported which in three generations showed a larger number.

A family case history is presented herewith which is unusual because of the high incidence of hypochromic anemia in one generation.

The first member of the family to be examined was seen at the age of 42. She sought medical advice at that time because of pain and weakness of the right thumb and swelling of the right wrist. A neurological examination revealed a probable amyotrophic lateral sclerosis which accounted for these subjective symptoms, and which may or may not have been related to a long standing anemia. Neurological examination was otherwise negative except for a loss of vibratory sense over the tibiae. There was no history of menorrhagia, metrorrhagia or other blood loss. She stated that at an examination 10 years before, namely, at the age of 32, she had been found to have an anemia, and reports obtained from the physicians who had attended her at that time showed that the hemoglobin had been 58 per cent, and the red count

3.5 million. Gastric analysis had revealed an absolute achlorhydria. Otherwise except for a palpable spleen the physical and laboratory findings had been essentially negative.

At the time of my examination this patient, at the age of 42, was found to have a hemoglobin of 65 per cent, with a red count of 3.8 million. A gastric analysis, with histamine, again showed an absolute achlorhydria.

The patient was observed for a number of years and her response to iron therapy was typical of this class of case. Although rather refractory to treatment her blood count, which at one time was as low as 2.5 million with a hemoglobin of 50 per cent, was, with large doses of iron, raised to a red count of four million and a hemoglobin of 70 per cent. This improvement was preceded by an increase in the reticulocyte count from 0.1 per cent to 0.6 per cent.

The family history of this patient is of greater significance than is the report of her own case. The patient was one of six sisters, there being no brothers. The mother died at the age of 52, after several attacks of "paralysis," probably due to cerebral accidents. Although no record of any blood count is available the patient stated that her mother was always considered anemic, as were two of her mother's sisters. The father was reported as living, and as having always been in good general health.

One sister, Miss G. S., had been examined in 1919 at the age of 35 (?), because of nervousness and a somewhat persistent diarrhea. She was found at this time to have a hemoglobin of 46 per cent, with a red count of 2.7 million. A gastric analysis showed a hypochlorhydria with a hydrochloric acid of 10 degrees. There was no demonstrable etiological factor found for the anemia. The stools were negative for pathogenic parasites, and there was no history of chronic blood loss.

A second sister, Mrs. A. T., was examined in 1928, at the age of 40 (?), and was found to have a hemoglobin of 50 per cent, with a red count of 3.9 million. Gastric analysis revealed an achlorhydria. An examination a year later showed the blood to be essentially the same with the achlorhydria persisting. At the time of this second examination she complained of a menorrhagia, but this was considered to be a coincidental factor, and her condition was diagnosed as idiopathic secondary anemia.

A third sister, Mrs. A. S., was examined in 1920, at the age of 32. She complained of a menorrhagia for which she received intrauterine treatments with radium. At that time her hemoglobin was reported as 46 per cent with a red count of 3.5 million. Unfortunately I have been unable to obtain any record of a subsequent blood count. Her medical report contains no notation of any gastric analysis.

A fourth sister, Miss M. S., was examined in 1930, at the age of 24. Her chief complaints at that time were rheumatism and general debility. She was found to have a hemoglobin of 62 per cent with a red count of 4.4 million. A gastric analysis was not done.

On the fifth sister, Mrs. T. S., there were no records available of any blood counts, although she has, like her mother and aunts, always been considered anemic. There is, in her case, no report of any chronic blood loss.

A summary of these reports is given in table 1. Only one member of this family has been seen by me personally; the records of the others had to be obtained by correspondence.* The examinations in several of the cases had been made without particular study of the type of anemia encountered. There is, therefore, no conclusive evidence that all of these sisters had a hypochromic achlorhydric anemia. Nevertheless the evidence strongly suggests this possibility and in three of the cases no other diagnosis seems

* Acknowledgment is made of the help and coöperation of Dr. H. Z. Giffin of The Mayo Clinic and others in furnishing me with the clinical records of these cases.

TABLE I
Blood Counts and Gastric Analyses of a Patient with Hypochromic Anemia and of Her Five Sisters

Name	Age	Hemoglobin (per cent)	RBC (Millions)	WBC	Differ- ential	Gastric Analysis
Miss F. S. . .	32	58	3.5	6,800	Normal	Achlorhydria
	42	70	3.25	4,000	"	"
Miss G. S. . .	35 ±	46	2.7	6,400	Normal	Hypochlorhydria HCl = 10°
Mrs. A. T. . .	40 ±	50	3.9	5,600	Normal	Achlorhydria
	41 ±	45	4.6	6,500	"	"
Mrs. A. S. . .	32	46	3.5	7,000	Normal	Not done
Mrs. M. S. .	24	62	4.4	7,600	Normal	Not done
Mrs. T. S. . .	No record of blood counts available but was "always considered anemic."					

possible. In spite of the deficiencies in the completeness of the record in some of the cases anemia was present in all, and there was an achlorhydria, or marked hypochlorhydria in all cases in which a gastric analysis was performed. No other factors were constant.

One other family is reported herewith which is of interest in this discussion because any conclusions that may be drawn are at variance with those just made.

Mrs. J. VS., at the age of 28, had sought medical attention because of a three months' pregnancy. At that time she is reported to have had a hemoglobin of 32 per cent with a red count of three million. She had an achlorhydria and splenomegaly, but otherwise negative physical findings. Out of six Wassermann tests taken in the preceding five years two had been found to be positive. Three more tests were taken, however, at this time, one following a provocative salvarsan, and all were negative. She was, nevertheless, started on neosalvarsan and possibly because of this stimulus her blood count improved slightly, the red count increasing to five million and the hemoglobin to 45 per cent. She had previously failed to respond to liver therapy. When I first saw her she was complaining of general weakness and looked markedly anemic; the tongue was somewhat smooth and the mucous membranes pale. The spleen was enlarged and palpable, and the liver edge was palpable and tender. On large doses of iron her reticulocyte count increased from 2 per cent to 3.5 per cent, her hemoglobin to 89 per cent, the red count still remaining normal. There has never been any apparent cause for her secondary anemia. The clinical manifestations and the response to therapy with iron would indicate that the anemia in this case is of the achlorhydric hypochromic type.

This patient's mother, who presented no subjective symptoms, was found to have a hemoglobin of 76 per cent, a red count of 4.1 million, and a white count of 5,600. Her two children, aged less than 10, presented essentially normal blood counts.

The patient's sister, Mrs. B. W., aged 33, said that she was found to have anemia five or six years before, and that as long as she could remember she had been nervous and tired. There was no history of metrorrhagia or other chronic blood loss. She was found to have a hemoglobin of 64 per cent, a red count of 2.5 million, and a white

count of 4,600. Her liver and spleen were not palpable, and there were no neurological changes. The gastric analysis, with histamine, revealed a normal hydrochloric acid secretion.

In this family we have a case of achlorhydric hypochromic anemia with the patient's mother and sister presenting, respectively, evidence of a mild and of a moderately severe idiopathic secondary anemia of undetermined origin. A summary of these findings is given in table 2. Although a

TABLE II

Blood Counts and Gastric Analyses of a Patient with Hypochromic Anemia and of Other Members of the Family

Name and Relationship	Age	Hemoglobin (per cent)	RBC (Millions)	WBC	Differential	Gastric Analysis
Mrs. J. VS.....	28	32	3			Achlorhydria
	28	42	5	4,200	Normal	"
(After treatment).....	32	89	4.8	9,800	"	
Mrs. B. W. (Sister)....	33	64	2.5	4,600	Normal	Normal
Mrs. S. (Mother).....	55 ±	75	4.1	5,600	Normal	Not done

hereditary or familial factor is suggested, there is no evidence that these three cases are related etiologically. The secondary anemias constitute a large and diversified group with overlapping morphological manifestations. Just as there was found to be not infrequently a coincidental occurrence of pernicious anemia and hypochromic anemia in the same families, so there may be a similar familial association of hypochromic anemia with other idiopathic anemias. Whether these hematopoietic disturbances could be caused by a common factor and whether this factor would be endogenous or exogenous is subject to conjecture only.

SUMMARY

1. A review of the literature and of case histories of hypochromic anemia with achlorhydria indicates that there is a not uncommon association of this type of anemia with primary anemia in members of the same family. A family history of secondary anemia of undetermined type is occasionally found, but proved reported cases of achlorhydric anemia in more than one member of a family are rare. I have found no record of more than two cases in one generation.

2. Of possible importance from the point of view of etiology is the evidence of a familial form of achlorhydria although there is no known relationship between this and achlorhydric anemia. The specific hematopoietic hormone of normal gastric juice recently demonstrated by Castle which is absent in pernicious anemia was found to be present in some cases of achlorhydric anemia. Nevertheless, nearly all contributors to the sub-

ject, from Faber who in 1913 first described the disease, to the most recent writers, advance the theory that the anemia is secondary to a gastric secretion deficiency which results in an interference with the maintenance of normal hematopoiesis.

3. A case history of achlorhydric hypochromic anemia is presented with actual or presumptive evidence of the same type of anemia in the patient's five sisters and in her mother and mother's sisters. There is nothing in the history or physical or laboratory findings of these individuals to suggest a common factor of etiological significance. A second family is reported where there seems to be a tendency to secondary anemia, but where only one case was of the achlorhydric achromic type. If these cases are related etiologically there is again no indication as to what the etiological factor may be. One may only conclude that this type of anemia is not uncommonly found in families in which there is evidence of primary or secondary anemia in other members of the same family.

REFERENCES

1. FABER, K.: Anämische Zustände bei der chronischen Achylia gastrica, Berlin klin. Wchnschr., 1913, I, 958-962.
2. WITTS, L. J.: Simple achlorhydric anemia, Guy's Hosp. Rep., 1930, lxxx, 253-296.
3. FRIEDENWALD, J., and MORRISON, T. H.: Clinical significance of achylia gastrica and achlorhydria, Internat. Med. Digest, 1932, xx, 244-250.
4. HURST, A. F.: Achlorhydria and achylia gastrica, and their connection with Addison's anemia—subacute combined with degeneration syndrome and simple (non-Addisonian), Quart. Jr. Med., 1932, i, 157-177.
5. WAUGH, T. R.: Hypochromic anemia with achlorhydria, Arch. Int. Med., 1931, xlvii, 71-81.
6. McCANN, W. S., and DYE, J.: Chlorotic anemia with achlorhydria, splenomegaly, and small corpuscular diameters, ANN. INT. MED., 1931, iv, 918-930.
7. HEATH, C. W.: Idiopathic hypochromic anemia with achlorhydria, Med. Clin. N. Am., 1932, xv, 1015-1024.
8. CASTLE, W. B., HEATH, C. W., and STRAUSS, M. B.: Observations on the etiologic relationship of achylia gastrica to pernicious anemia, Am. Jr. Med. Sci., 1931, clxxxii, 741-764.
9. MORRIS, R. S., SCHIFF, L., BURGER, G., and SHERMAN, J. E.: Specific hematopoietic hormone in normal gastric juice, preliminary note, Jr. Am. Med. Assoc., 1932, xcvi, 1080-1081.
10. WINTROBE, M. M., and BEEBE, R. T.: Idiopathic hypochromic anemia, Medicine, 1933, xii, 187-243.

TUBERCULOMA OF THE BRAIN *

By MAURICE LEWISON, M.D., F.A.C.P., ELLIS B. FREILICH, M.D., and
OSCAR B. RAGINS, M.D., *Chicago, Illinois*

IN AN analysis of 757 autopsies performed at the Cook County Hospital from 1917 to 1927 inclusive, on patients who had died of tuberculosis, 20 instances of the occurrence of tuberculoma of the brain were discovered. It is the purpose of this paper to present briefly certain clinical and pathologic data which have been drawn from the records of these cases. In some instances desired information has not been available. This is due in part to the fact that the condition was not usually suspected during the patients' life time, only two cases having been diagnosed ante mortem.

The literature of tuberculoma of the central nervous system is fairly extensive. Recently Anderson ¹ has published an excellent review, together with a report on 27 cases, the largest single series reported.

The pathology of tuberculoma of the brain is essentially the same as that of a tuberculous lesion elsewhere. What is spoken of frequently as solitary tubercle of the brain is in reality an aggregation of many small tubercles with caseous fusion of the originally discrete lesions. Occasionally sclerosis is observed in the vicinity of tuberculoma masses. It may be constituted of proliferated glial cells or it may arise from proliferation of the adventitia of neighboring blood vessels.

From the point of view of symptomatology the cases fall into two groups. In the first the symptoms are those of a space-occupying mass in the cranial cavity or spinal canal, i.e., the symptoms of increased intracranial pressure plus those further localizing symptoms and signs which indicate the level of the lesion. In the second group of cases the outstanding clinical symptoms are those due to the coincident tuberculous meningitis; and these meningeal symptoms frequently completely mask the clinical evidences of the presence of tuberculoma.

In table 1 are given the symptoms referable to the nervous system which were present in our 20 cases on admission to the hospital. In the majority of these cases the symptoms indicated the presence of a meningitis. In seven the clinical diagnosis of tuberculous meningitis was made. In two instances tuberculoma of the brain was diagnosed. At autopsy meningitis was found in 17 cases, in one case a focal meningitis was reported, and in two cases the meninges did not show any involvement.

The sites in the brain at which the tuberculomas were found at autopsy do not indicate any special predilection of this lesion for any certain area. The incidence was somewhat higher in the left side of the brain than in the right. The number of tuberculomas found varied considerably, though over half of the cases showed a solitary lesion. There were 11 cases with

* Received for publication November 13, 1933.

TABLE I
Data of 20 Cases of Tuberculoma of Brain

No. of Cases	Age	Sex	Color	Symptoms Referable to C.N.S.	Spinal Fluid	No. of Tuberculomas	Location of Tuberculomas	Meningitis	Clinical Diagnosis	Tuberculosis in Other Organs of the Body
1	4	M.	C.	Neck rigidity, headache, vomiting	Increased pressure and globulin	3	Corpus callosum, rt. parietal lobe, left temporal lobe	Present	Miliary tuberculosis	Miliary tbc. lungs, liver, spleen, and kidneys; caseous tbc. adrenals.
2	30	F.	C.	Vomiting, pain in head		1	Rt. parietal lobe	Absent	Tuberculous meningitis; pelvic peritonitis and salpingitis	Caseous tbc. of fallopian tubes.
3	29	M.	C.			1	Left temporal lobe	Present	Pulmonary tuberculosis	Bil. ulc. caseous pulmonary tbc.; nodular tbc. liver and spleen; tbc. cervical and mediastinal glands.
4	17	M.	C.	Headache	Increased pressure and globulin	2	Rt. temporal lobe, rt. middle cranial fossa	Present	Acute miliary tuberculosis; generalized skeletal tuberculosis	Tbc. pleuritis; extensive skeleton tuberculosis.
5	34	F.	C.	Headache		2	Cerebellum, basal ganglia	Present	Pulmonary tuberculosis	Miliary tbc. lungs, spleen, liver, kidneys; caseous tbc. fallopian tubes.
6	4	W.		Comatose or stupor	Increased pressure and globulin	1	Rt. temporal lobe	Present	None given	Miliary tbc. lungs; tbc. entero-colitis.

TABLE I (Continued)

No. of Cases	Age	Sex	Color	Symptoms Referable to C.N.S.	Spinal Fluid	No. of Tuberculomas	Location of Tuberculomas	Men- gitis	Clinical Diagnosis	Tuberculosis in Other Organs of the Body
7	16	M.	C.	Neck rigidity		Small multiple tuberculomas	Various parts of brain	Present	Tuberculous meningitis	Miliary tbc. lungs, pleura, pancreas, liver, spleen, ureters, bladder; tbc. abscess of small intestines.
8	15 mo.	M.	C.		Increased pressure and globulin	1	Left cerebral hemisphere	Present	Tuberculous meningitis	Miliary tbc. lungs, liver, and spleen.
9	56	M.	C.	Headache, neck rigidity	Increased pressure and globulin	1	Left cerebral hemisphere	Present	Tuberculous meningitis	Miliary tbc. lungs, liver, spleen, and kidney; tbc. ulcers of colon.
10	5	F.	C.	Vomiting, neck rigidity, headache pain over lt. eye	Increased pressure and globulin	1	Left cerebral hemisphere	Present	Tuberculoma; tuberculous meningitis	Caseous tbc. mediastinal and mesenteric lymph glands.
11	4	F.	Mex.	Headache		1	Left cerebral hemisphere	Present	Pulmonary tuberculosis	Ultero-caseous pulmonary tbc.; ulcers of large and small intestines.
12	12	F.	C.	Gradual loss of vision; headache	Increased pressure and globulin	1	Base of brain	Present	Tuberculoma? Tuberculous meningitis	Tbc. osteitis of sella turcica, and tracheobronchial lymph glands.
13	45	M.	C.			Multiple	Cerebellar lobes	Present	Pulmonary tuberculosis; tuberculosis of sacro-iliac joint	Pul. ultero-caseous tbc.; tbc. osteitis of sacro-iliac joints; caseous tbc. adrenal and genitourinary organs.

TABLE I (Continued)

No. of Cases	Age	Sex	Color	Symptoms Referable to C.N.S.	Spinal Fluid	No. of Tuberculomas	Location of Tuberculomas	Menin- gitis	Clinical Diagnosis	Tuberculosis in Other Organs of the Body
14	5	F.	W.	Vomiting; headache	Increased pressure and globulin	3	Right temporal lobe, inferior oc- cipital lobe and pons	Present	Tuberculous men- ingitis	Pul. ulcero-caseous tbc.; tbc. pleura, pericar- dium.
15	42	F.	?	Vomiting; headache	Increased pressure	1	Right cerebellar lobe	Focal menin- gitis	Cerebello-pontine angle tumor	Tbc. osteitis of middle cranial fossa.
16	28	M.	C.			1	Pons; tuberculous abscess	Absent	Cerebro-spinal syphilis	Tbc. left apex; tbc. peritonitis.
17	2½	M.	C.	Rigidity of neck		1	Cerebellum	Present	Encephalitis	Broncho-pneumonic pulmonary tbc.; miliary tbc. liver, spleen, and kidney.
18	3	F.	C.			Multiple	Cerebrum and cerebellum	Present	Hydrocephalus	Tbc. ulcers of rectum; caseous tbc. uterus and fallopian tubes.
19	45	F.	C.	Nausea; headaches	Increased pressure; Wassermann ++	2	Not stated	Present	Cerebro-spinal syphilis	Bilateral ulcero-caseous tbc.; caseous tbc. medi- astinal and abdominal lymph glands; miliary tbc. liver, spleen, and parametrium.
20	24	M.	Mex.			2	Rt. parietal lobe, and cerebellum	Present	Epidemic menin- gitis	Miliary tbc. lungs, liver, spleen; caseous tbc. tracheo-bronchial lymph glands.

one tuberculoma, four cases with two, two cases with three, and three cases with multiple tuberculomas.

In all of these 20 cases tuberculous lesions were found in other organs of the body in addition to the lesions of the brain. The occurrence of brain tuberculoma in the various clinical types of tuberculosis in our series is shown in table 2.

TABLE II

Clinical Type of Tuberculosis	No. of Cases	Incidence of Tuberculoma
Pulmonary tuberculosis	482	4
Miliary tuberculosis	96	1
Tuberculous meningitis	146	12
Tuberculous peritonitis	32	2
Addison's disease	1	1

The youngest case in our series was 15 months and the oldest 56 years. The average age was 22.7 years. It was predominantly an adult group. This age incidence in our series is of interest since it is often stated that brain tuberculoma occurs with greatest frequency in childhood. There was an equal number of males and females in the group. There were 16 cases in colored patients, two in white and two in Mexicans. The high proportion of colored patients is perhaps significant.

CONCLUSIONS

1. Twenty instances of tuberculoma of the brain were discovered in 757 autopsies of tuberculous patients.

2. The clinical signs and symptoms of meningitis frequently masked the tumor syndrome which may be presented by these cases.

3. The average age in these 20 cases was 22.7 years: it was a predominantly adult group.

4. Nearly one-half (45 per cent) of these cases showed the presence of more than one tuberculoma.

5. All parts of the brain seem equally subject to the development of tuberculoma.

6. Tuberculous foci in other portions of the body were uniformly present.

REFERENCE

1. ANDERSON, F. N.: Tuberculoma of central nervous system, *Arch. Neurol. and Psychiat.*, 1928, xx, 354-365.

EDITORIALS

WHAT constitutes leadership in medicine? Leadership is the ability to inspire a desire for improvement and the willingness to work to that end. A leader in medicine not only gives instruction but makes of that instruction an inspirational force that leads the listener to study for himself and to remain ever unsatisfied with his own knowledge. Inspirational leadership in medicine comes largely from a personal magnetism in one with a broad knowledge of the science and art of medicine. To get it one must see and hear the leader. Reading what he writes falls short of inspiration. This is why we go to medical meetings. How much easier to stay at home and read the published paper, but how much less vivid, less stimulating, less worth while is it to read rather than to hear and see the leader in his presentation of a medical topic.

HENRY A. CHRISTIAN, M.D., F.A.C.P.

PSYCHOANALYSIS

OF WHAT use, in the treatment of the patient, is psychoanalysis? This is a question which must have occurred to many a physician. Nor can he readily find a dependable answer. It is by results, especially end-results, that we should judge the merit of any form of therapy. Because of scarcity of such information in the case of therapeutic psychoanalysis, physicians have assumed an attitude toward that procedure all the way from open hostility to wild enthusiasm, with hostility or indifference predominating.

That many physicians should look askance at psychoanalysis is due in part to the seeming bizarreness of some of the tenets of the cult, and in part to doubt as to the good sense and judgment of the analysts. Certain affectations on their part shake confidence. When, as a group, they attain to greater maturity, they will inspire more faith. The young analyst is often a zealot. Like a convert to a new religion, he becomes narrowly sectarian. The strict Freudian sees no good in heterodox activities. This is all rather a pity because unquestionably psychoanalysis has much that should be of vital interest to the physician.

There are at least three purposes to which psychoanalysis can be put. These are psychological research, education and therapeutics. Of its value in the first of these, there can be no doubt. In the exploration of the human mind the psychoanalytical technic has penetrated new depths. It has revolutionized our notions of mental anatomy. Also, in education, it has proved its worth. For those who seek to solve problems of personality, a true knowledge of self is indispensable. It is well for any type of psychodiagnostician or therapist to know his own blind spots, conflicts and prejudices. It may be accepted that these can be discovered more completely by psychoanalysis than in any other way.

There still remains, however, for the practicing physician the question: has psychoanalysis any place in the actual care of the sick? Only data upon the outcome in clinical cases can truthfully answer this question. The recent paper of Kessel and Hyman* is very important because it contains such information. These physicians referred certain patients to psychoanalysts and observed whether the analysis accomplished the purpose for which it was undertaken. In slightly over 50 per cent of their cases, patients were helped; in 15 per cent they obtained cures which they regarded as specific, that is to say obtainable in no other way. It is upon the basis of data of this kind that physicians will ultimately achieve a sound evaluation of the method. It is to be hoped that much more will presently be published, and that, too, in the journals commonly read by clinicians.

That 15 per cent of "specific" cures were obtained by Kessel and Hyman is ground for looking upon the treatment as important. That not a greater percentage of the cases treated gave good results indicates either that the treatment was poorly given or that the patients were badly selected. Improvement in technic is a problem for the analyst. Improvement in the selection of cases is a problem for the physician.

At the present time we have but few guides to selection. Patients will fall, of course, for the most part in the general group of so-called neurotics or poorly adjusted persons. Also, it seems clear that a high degree of intelligence is a requisite, and that the patient be not too old; also that he have an understanding of the nature of the technic and a willingness to be analyzed. But we need far more explicit guides than these in selecting cases.

The availability of the treatment is a very large factor. The orthodox analysis is very time-consuming and expensive, and on that ground alone impossible for many persons who seemingly may need it. In a general hospital or dispensary, because of its very cumbersomeness, it is useless as a form of routine treatment for patients of a certain type.

In hospitals, however, where clinical research is done, psychoanalysis will find its place. It will be used not for the immediate purpose of curing patients, though it may do that, but to widen our knowledge of disease. It may be expected, through the increased understanding it gives us of the nature of disease, to permit improvements in many forms of therapy. We shall understand the patient and his reactions to his disease better in the light of knowledge gained through psychoanalytical research, and so be able to treat him better, even though formal therapeutic analysis is used but seldom or not at all. It is likely that new forms of treatment will emerge, the sort that Stekel† calls active analysis, in contrast to the passive type of the orthodox school, which while preserving the essence of the analytic theory will be so simple and direct as to be available to the host of patients

* KESSEL, L., and HYMAN, H. T.: The value of psychoanalysis as a therapeutic procedure, *Jr. Am. Med. Assoc.*, 1933, ci, 1612.

† STEKEL, W.: The future of psychoanalysis (translation by L. S. LONDON). *Psychoanalytic Rev.*, 1933, xx, 327.

needing such treatment, but to whom formal analysis is barred. Also, as Stekel brings out, the psychoanalytic type of understanding may come to permeate all medical practice. It will become the possession of all physicians, not merely of a small group of specialists. Because of all this, it is greatly to be desired that physicians substitute, for an attitude of hostility or indifference, one of active interest, careful checking of results, and finally constructive criticism.

JAMES H. MEANS

REVIEWS

Metabolic Diseases and Their Treatment. By ERICH GRAFE; translated by MARGARET GALT BOISE, under the supervision of EUGENE F. DuBOIS, M.D., and HENRY B. RICHARDSON, M.D. xii + 551 pages; 16 x 24 cm. Lea and Febiger, Philadelphia. 1933. Price, \$6.50.

It is a genuine pleasure to welcome the appearance of an English translation of this well-known German work on the diseases of metabolism. The material has been carefully selected and attractively presented. The references are abundant, judiciously chosen, and generally accurate. The German literature is naturally widely covered, but the important American and French work is also well represented and properly appraised and credited. Throughout the book the author displays exceptional powers of lucid yet pithy exposition. The sections of the book on obesity and on diabetes are of particular interest. There are fundamental differences from the orthodox American conceptions, particularly as regards therapy, and many of these are stimulating and refreshing. That many will be inclined to differ sharply from the author in matters of detail is quite evident, but this in no way detracts from the educational value of this book. Dr. DuBois and Dr. Richardson have done a valuable service by their careful supervision of this excellent translation. It seems to the reviewer that it is one of the best textbooks on disorders of metabolism which has appeared in recent years. He will have no hesitation in recommending the book to students as probably the best short treatise available at the present time in the field of metabolic diseases.

G. A. H.

Behind the Doctor. By LOGAN CLENDENING. xxviii + 458 pages; 16.5 x 24 cm. Alfred A. Knopf, New York. 1933. Price, \$3.75.

The Great Doctors. By HENRY E. SIGERIST; translated from the German by EDEN and CEDAR PAUL. 436 pages; 15 x 22 cm. W. W. Norton, New York. 1933. Price, \$4.00.

It seems that every one who touches medical history, whether he be a mere dabbler or a university professor of the subject, is immediately seized with a desire to write a popular book on the subject. There have been many of such books of late years, some good, some bad and some indifferent. It is no mean task to try to compress the whole of medical history in a few pages and to make it understandable and interesting to a layman, and it requires peculiar talents which the authors of both the above books are fortunate enough to possess.

The first is written by a master of journalese, who has gleaned many an interesting tale from the past and made a book which will delight not only the doctor familiar with medical history, but also the one who knows nothing about it and the layman who wishes to know something of what lies behind the doctor. To the last it will come as a revelation and it reads like a thrilling, best selling novel. The subject of the healing art from the medicine of primitive man to the modern doctor with his vitamins and roentgen-rays and his new chemicals is satisfactorily covered, especially from a layman's standpoint. The tale is told with great gusto and imaginary conversations enliven what otherwise might be a mere recital of facts. The paragraphs are short and the tempo of the book *allegro con moto* and at times *prestissimo*. The book is profusely illustrated with, for the most part, well chosen pictures, portraits, and drawings. Many of them unfortunately are poorly reproduced.

The second book is a biographical history of medicine and the story is told around the lives of 48 men whom Sigerist evidently thinks either the most interesting or the

most important. It was originally written in German but the translators, old hands at the game, have done a good job.

In his preface, the author forestalls any criticism of his choice of the men he has portrayed and that certainly is his affair, but many estimates seem strange. Soranus comes in for his share of the book, but no mention is made of his pediatric text which is perhaps the best of the ancient ones and two-thirds correct, judged by present-day standards. Roentgen, who changed modern diagnosis, gets but a short paragraph. In the German edition no Americans are given any more than a passing notice and in the second only Osler is added as a sort of sop to American readers. Morton and anesthesia; Walter Reed and his co-workers and Gorgas making the tropics safe for white men; Beaumont and his contribution to physiology; Halsted and his work especially local anesthesia, Marion Sims, O'Dwyer and many others would seem worthy enough to be the center of a chapter. The book is interesting, chiefly as an exposition of the views of one of the most eminent living medical historians, and his estimates and how he adjudges the great men of the past are not to be taken lightly. The illustrations are excellent and well produced. Both books contain extensive bibliographies and it is striking how both, using different sources, have given essentially the same picture of Vesalius and his achievements, good evidence of the crystalization of our knowledge of the man and his work. Both books may be recommended.

J. R.

Die Venarum Ostiolis, 1603, of Hieronymus Fabricius of Aquapendente (1533?-1619). Translated by E. J. FRANKLIN, D.M. 98 pages; 16.5 x 25 cm. Charles C. Thomas, Springfield. 1933. Price, \$3.00.

Here is a book to delight the heart of the bibliophile, a facsimile edition of this comparatively little known work with an introduction, translation and notes by one who knew what he was about. The valves in the veins had been noted before but no one had paid much attention so that Fabricius deserves the credit of putting them before the profession. Among his many students in anatomy was William Harvey; the valves in the veins set him thinking and the result was his discovery of the circulation of the blood. It is a well planned book containing a biography, a history of the early work on the venous valves, an account of the theatre of the school of anatomy at Padua and some extremely useful bibliographical notes. The original plates have been reproduced. Every library should have this book and also every one interested in the history of medicine. It is beautifully printed on good paper and is a credit both to Dr. Franklin and to the publisher.

J. R.

Mental Hygiene in the Community. By CLARA BASSETT. The Macmillan Company, New York. 1934. Price, \$3.50.

Mental Hygiene in the Community, published in January 1934, is written by one trained and experienced in psychiatric social work. It is a panoramic exposition of available data aiming to present in brief and correlated form the various ways in which mental hygiene may be of importance and value, and where it may profitably function in the present organization of community life. The book should stimulate interest and encourage experimentation for meeting local mental health needs and situations. Each chapter contains pertinent suggestions for preliminary study and investigation of specific phases of the problem and illustrations of methods that are applicable for experimentation.

The author views the present status of mental hygiene as being unable to offer definite and concrete solutions for the many problems involving the amelioration, treatment, or cure of the multiple adverse mental and personality situations or their prevention; or the promotion of positive mental health, the latter depending on forces

lying partly outside the question of illness and its avoidance. The contributions that law, psychology, sociology, education in its broadest sense, or public policies must make in the latter field cannot avoid the fundamental place which modern medicine occupies or may be expected to occupy in the future, for the promotion of good mental health implies a knowledge of factors influencing the nature, causation, and prevention of ill health. Her approach to these yet unsolved problems is based on healthy appreciation of the present status of mental hygiene and she clearly depicts the situation thus: "From the standpoint of pure science, mental hygiene is hardly out of its swaddling clothes and many more decades of research and experimentation will be necessary before such a happy consummation will be achieved. The evolution of every science and art has been a slow fumbling and stumbling toward the light of truth; and mental hygiene is no exception to this rule. The only development possible is through the conscientious application of the best knowledge available at the moment, followed by a keenly critical appraisal of the accumulated experience and results obtained, which in turn brings about modifications in theory and practice so that these are ever more closely in accord with the facts and needs of the situation. Through this process mental hygiene will gradually emerge from the haze of conflict which envelops the various schools of thought, its theories will be more precisely defined, clarified, consolidated and tested and a more and more effective instrument for the study, treatment and prevention of mental and behavior disorders will be forged."

The book, comprising twelve chapters with index and list of bibliographies, lends itself to convenient assignments in reading courses or text study. The first chapter consists of introduction to the subject; the second a discussion of medicine with special reference to the recognition that every form of illness has a psychic component, and to the need for graduate and undergraduate instruction. The third chapter discusses the position of nursing in the field; the fourth the place of social service agencies, followed by other chapters devoted to the subjects of delinquency and law, parental education, the pre-school child, education and teacher training, the church and theological training, industry, recreation, and psychiatric institutions and agencies.

W. L. T.

The Lyophilic Colloids (Their Theory and Practice). By MARTIN H. FISCHER, Professor of Physiology in the University of Cincinnati, and MARIAN O. HOOKER, Research Associate in Physiology in the University of Cincinnati. Ed. I. iii + 246 pages; 16 x 25 cm. Charles C. Thomas, Springfield, Ill. 1933. Price, \$4.50.

The increasing importance of colloid chemistry in the field of experimental physiology bespeaks the timely nature of a treatise of this kind from the pen of the first author and his associate. This book summarizes the investigations of the authors in colloid chemistry which have extended over a period of fifteen years.

The book is divided into three parts. Part one deals with the "General Nature of the Lyophilic Colloid"; part two, points out the "Chemical Applications" and part three considers the "Biological Applications."

The subject matter of part one consists of a description of the physical and chemical properties of various lyophilic colloid systems, such as phenol water, gelatin water and casein water. Many tables and photographs are included to illustrate the subject matter under discussion. The theoretical aspects of the subject are most interestingly treated by the authors.

Part three is of special interest to the readers of this journal. The osmotic concept of the living cell is critically examined. Edema is discussed as a problem in colloid chemistry along with several very important practical suggestions on acidosis and alkalosis. The authors warn against persistence in attempting to show that the

physicochemical laws of dilute solutions apply to biological phenomena. They prefer considering these solutions in cells as "solutions of the inverse type." They state: "When we have discovered their laws, when we have familiarized ourselves with the physicochemical and colloid-chemical behavior of systems of the type water-dissolved-in- x , we shall find ourselves possessed also of the laws which govern the behavior of protoplasm under physiological and pathological circumstances."

J. C. K., JR.

Diet and Personality. Fitting Food to Type and Environment. By L. JEAN BOGERT, Ph.D.; with an introduction by LAFAYETTE B. MENDEL, Ph.D., Sc.D., Sterling Professor of Physiological Chemistry, Yale University. ix + 223 pages; 14 x 20 cm. Macmillan Co., New York. 1934. Price, \$2.00.

This is a book giving popular medical advice, written by a non-medical author. The advice is not confined to diet alone, but includes many topics, such as a discussion of exercise, rest, fresh air, sunshine, nervous strain, smoking, bathing, posture, hours of sleep, and care of the teeth and bowels. It is written in the chatty, semi-facetious style which has had so great a vogue among books of this character during the past few years. There is nothing that is new or original in this book, or that has not been better done in a number of its predecessors.

G. A. H.

PROGRAM
EIGHTEENTH ANNUAL CLINICAL SESSION
OF THE
AMERICAN COLLEGE OF PHYSICIANS

Chicago, Ill., April 16-20, 1934

George Morris Piersol, President
General Sessions

James B. Herrick, General Chairman
Clinical Program

E. R. Loveland, Executive Secretary
133-135 South Thirty-Sixth Street
Philadelphia, Pa.

COMMITTEE ON ARRANGEMENTS

James B. Herrick, Chairman

Joseph A. Capps
Anton J. Carlson
Anders Frick
Julius H. Hess

Samuel E. Munson
S. R. Pietrowicz
Francis E. Seneer

COMMITTEE ON CLINICS

Arthur R. Elliott, Chairman

Robert S. Berghoff
Mercy Hospital

Hugh A. McQuigan
University of Illinois College of
Medicine and Hospitals

Joseph Brennemann
Children's Memorial Hospital

Henry T. Ricketts
University of Chicago Medical
School and Hospitals

Charles A. Elliott
Northwestern University Medical
School, Passavant Memorial and
Wesley Hospitals

Solomon Strouse
Michael Reese Hospital

George W. Hall
St. Luke's Hospital

Frederick Tice
Cook County Hospital

Allan J. Hrubby
Chicago Municipal Tuberculosis
Sanitarium

Italo F. Volini
Loyola University School of Medi-
cine

Ernest E. Irons
Rush Medical College, Presbyterian Hospital

COMMITTEE ON HOTELS, AUDITORIUM
AND TRANSPORTATION

LeRoy H. Sloan, Chairman

Italo Volini

Sidney A. Portis

COMMITTEE ON PUBLICITY

Malcolm T. MacEachern, Chairman

James G. Carr
Nathan S. Davis, IIIJosiah J. Moore
Willard O. Thompson

COMMITTEE ON ENTERTAINMENT

John Favill, Chairman

George H. Coleman

Julius H. Hess

COMMITTEE ON ENTERTAINMENT OF VISITING WOMEN

Mrs. Nathan S. Davis, III, Chairman

Mrs. Clifford J. Barborka
Mrs. Robert S. Berghoff
Mrs. Joseph A. Capps
Mrs. James G. Carr
Mrs. George H. Coleman
Mrs. Arthur R. Elliott
Mrs. Charles A. Elliott
Mrs. John Favill
Mrs. A. A. Goldsmith
Mrs. Leo L. Hardt
Mrs. Harry M. Hedge
Mrs. James B. Herrick
Mrs. Julius H. Hess
Mrs. A. L. Hoyne
Mrs. M. J. Hubeny
Mrs. James H. HuttonMrs. Ernest E. Irons
Mrs. Andrew C. Ivy
Mrs. Gustav L. Kaufmann
Mrs. George B. Lake
Mrs. Arthur E. Mahle
Mrs. Hugh A. McQuigan
Mrs. Joseph L. Miller
Mrs. Josiah J. Moore
Mrs. Benjamin H. Orndoff
Mrs. Milton M. Portis
Mrs. Francis E. Senear
Mrs. LeRoy H. Sloan
Mrs. Solomon Strouse
Mrs. Henry C. Sweany
Mrs. Willard O. Thompson
Mrs. Frederick Tice

Mrs. Italo F. Volini

GENERAL AND HOTEL HEADQUARTERS: PALMER HOUSE

State and Monroe Sts., Chicago

Registration headquarters, information bureau, railroad office, exhibits and the general assembly hall are all located here.

Rates per day, European Plan:

Palmer House

Single room with bath	\$ 3.50 to \$ 7.00
Double room, twin beds, with bath	6.00 to 11.00
Suites	14.00 up

(List of other Chicago Hotels will be published in the formal program)

WHO MAY REGISTER—

- (a) All members of the American College of Physicians in good standing for 1934.
- (b) All newly elected members.

- (c) Members of the Chicago Medical Society and of the Chicago Institute of Medicine, without registration fee, upon presentation of their 1934 membership cards.
- (d) Medical students pursuing courses at the University of Chicago Medical School, the University of Illinois College of Medicine, Northwestern University Medical School, Loyola University School of Medicine and the Rush Medical College, without registration fee, upon presentation of matriculation cards, or other evidence of registration at these institutions.
- (e) House Officers of the hospitals participating in the program, upon presentation of proper identification.
- (f) Members of the Medical Corps of the Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials.
- (g) Qualified physicians who may wish to attend this Session as visitors. Such physicians shall pay a registration fee of \$12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

REGISTRATION BUREAU.—Located at the entrance to the Exhibit Room on the Fourth Floor of the Palmer House. Hours: 8:30 a.m. to 6:00 p.m., daily, April 16-20.

REGISTRATION BLANKS FOR ALL CLINICS AND DEMONSTRATIONS will be sent with the program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

TRANSPORTATION.—Round trip tickets will be available on the basis of one and one-third of the current one-way first-class fares, with minimum excursion fare of \$1.00 for the round trip, upon presentation of identification certificates to be procured from the Executive Secretary of the American College of Physicians. The reduced fares will apply for physicians and dependent members of their families.

Members are privileged to make the going journey by one route and return by another route. Stop-overs will be allowed at all stations within final limit on either going or return trip, or both, upon application to conductors.

Before purchasing tickets, members must secure from the Executive Secretary an Identification Certificate, to entitle them to the reduced fares.

In general, tickets will be sold from April 10 to April 18, depending upon the relative distance from Chicago, with a return limit of thirty days in addition to date of sale.

All tickets must be validated by a special railroad agent at the Chicago Headquarters from April 16 to 20.

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 5:00 p.m., Thursday, April 19, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, the reports of the Treasurer and of the Executive Secretary, and the induction to office of the new President, Dr. Jonathan C. Meakins, Montreal, Que.

SPECIAL FEATURES

Monday, April 16, 1934

THE ANNUAL SMOKER.—Immediately following the scientific program, at about 10:20 o'clock, Monday evening, in the Red Lacquer Room of the Palmer House. An unusual program of entertainment, both amusing and instructive, will be presented.

Wednesday, April 18, 1934

CONVOCATION OF THE COLLEGE.—8:00 o'clock, Grand Ballroom, Palmer House. All Masters and Fellows of the College and those to be received in Fellowship should be present. Newly elected Fellows who have not yet been received in Fellowship are requested to occupy the central section of seats especially reserved for them. As this is the most formal meeting of the College, it is suggested that all appear in evening dress.

The Convocation is open to all physicians and their families generally, and to such of the general public as may be interested.

Following the Convocation Ceremony, the President of the College will deliver the annual Presidential address to the Masters, Fellows and Associates. Dr. Grant Fleming, Director of the Department of Public Health and Preventive Medicine, McGill University, Montreal, will deliver an address on "The Medical Aspects of National Health Insurance."

The Presidential Reception will follow immediately after the program. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the interim between the Convocation and the Reception. Dancing in the Red Lacquer Room.

THE EXPOSITION AND COMMERCIAL EXHIBIT will be located in the Exhibit Hall of the Palmer House.

Exhibits consisting of medical literature and texts, pharmaceutical products, apparatus and appliances, special foods, etc., will be shown by leading publishers and manufacturers. These exhibits afford an opportunity for physicians to examine the latest literature and the newest products in the field of medicine generally; their educational value should not be overlooked. Every attendant at the Session is urged to visit each of the booths, for he cannot help but find something new, interesting and scientifically valuable. Intermissions in the general program have been arranged from Tuesday to Friday, inclusive, for the purpose of providing a definite time for the inspection of exhibits.

COMMERCIAL EXHIBITORS

(The following is a partial list of exhibitors who have engaged space at the Eighteenth Annual Clinical Session of the American College of Physicians, Chicago, Ill.)

	<i>Space</i>
Abbott Laboratories, North Chicago, Ill.....	51
American Agency of French Vichy, Inc., New York, N. Y.....	55
Appleton-Century Company, D., New York, N. Y.....	68
Ayerst, McKenna & Harrison, Limited, Montreal, Que.....	16
Battle Creek Food Company, The, Battle Creek, Mich.....	13
Becton, Dickinson & Co., Rutherford, N. J.....	62
Betz Company, Frank S., Hammond, Ind.....	20
Bilhuber-Knoll Corp., Jersey City, N. J.....	60
Burdick Corporation, The, Milton, Wis.....	36-37
Cambridge Instrument Co. Inc., New York, N. Y.....	56
Cameron Surgical Specialty Co., Chicago, Ill.....	18
Chappel Bros. Inc., Rockford, Ill.....	22
Chicago Dietetic Supply House Inc., The, Chicago, Ill.....	28
Collins, Inc., Warren E., Boston, Mass.....	9
Corn Products Refining Co., New York, N. Y.....	17
Davies, Rose & Co., Ltd., Boston, Mass.....	50
Davis Company, F. A., Philadelphia, Pa.....	4

Eighteenth Annual Clinical Session

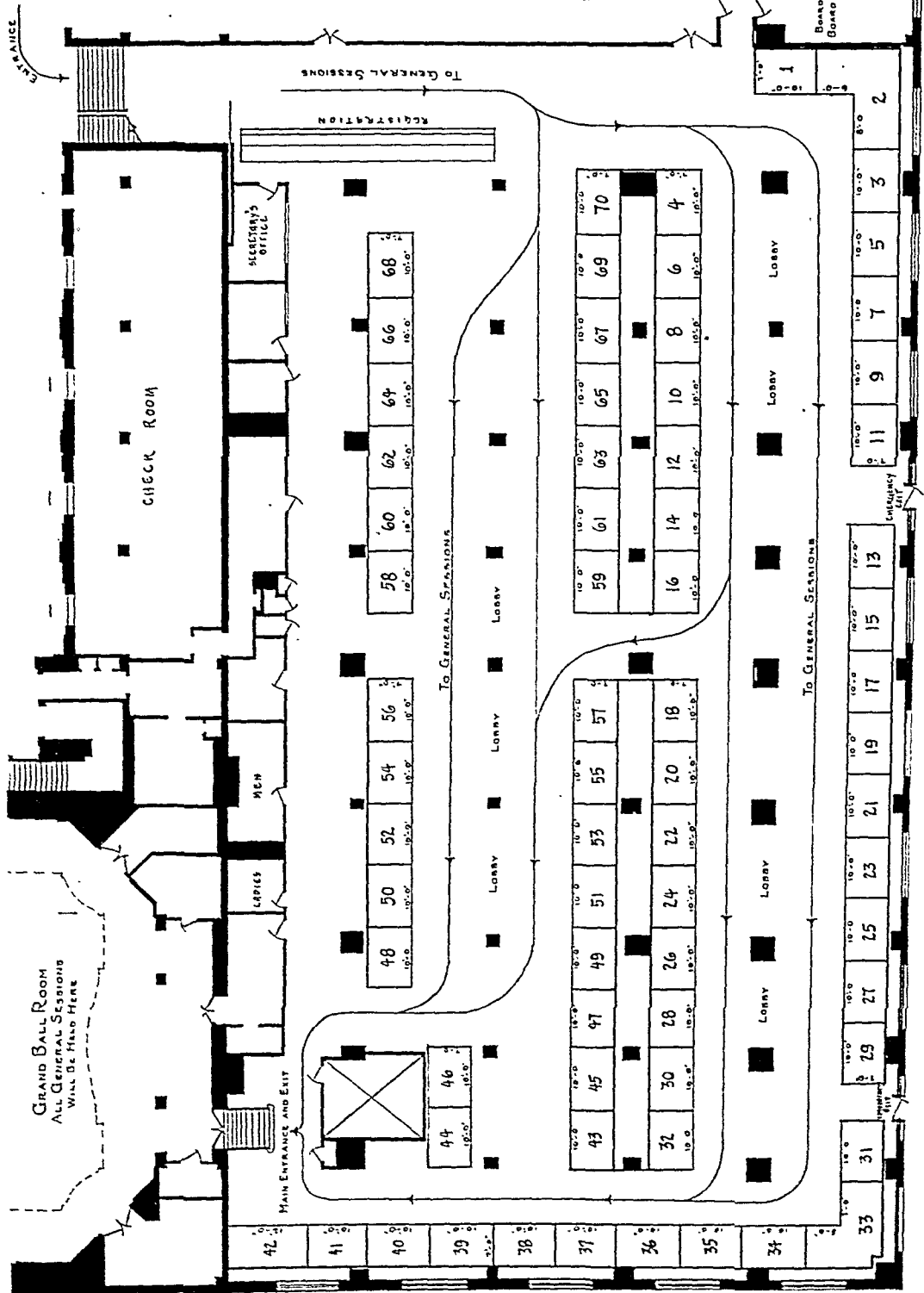
AMERICAN COLLEGE
OF PHYSICIANS

Palmer House

Chicago, Ill.

April 16-20, 1934

(See opposite page for list of exhibitors)



Davis Company, R. B., Hoboken, N. J.....	53
Doak Company, The, Cleveland, Ohio.....	57
Fougera and Co. Inc., E., New York, N. Y.....	8
General Electric X-Ray Corporation, Chicago, Ill.....	1-2-3-5
General Mills Inc., Minneapolis, Minn.....	31
Gerber Products Company, Fremont, Mich.....	42
Gradwohl School of Laboratory Technique, St. Louis, Mo.....	61
Hamilton Manufacturing Co., Two Rivers, Wis.....	34-35
Health Products Corporation, Newark, N. J.....	65
Hynson, Westcott & Dunning, Inc., Baltimore, Md.....	14
Kalak Water Co. of New York, Inc., New York, N. Y.....	32
Kellogg Company, Battle Creek, Mich.....	45
LaMotte Chemical Products Company, Baltimore, Md.....	58
Lea & Febiger, Philadelphia, Pa.....	52
Lederle Laboratories Inc., New York, N. Y.....	38
Lippincott Company, J. B., Philadelphia, Pa.....	69
Login Brothers, Chicago, Ill.	19
M & R Dietetic Labs., Inc., Columbus, Ohio.....	63
Macmillan Company, The, New York, N. Y.....	70
Maltine Company, The, New York, N. Y.....	48
Mead Johnson & Co., Evansville, Ind.....	33
Medical Bureau, The, Chicago, Ill.....	7
Medical Case History Bureau, New York, N. Y.....	43
Merck & Co. Inc., Rahway, N. J.	64-66
Metz Laboratories, Inc., H. A., New York, N. Y.....	41
Merrell Company, The Wm. S., Cincinnati, Ohio.....	30-44
Middlewest Instrument Company, Chicago, Ill.....	39
Mosby Company, The C. V., St. Louis, Mo.....	12
Petrolagar Laboratories, Inc., Chicago, Ill.....	67
Phillips Chemical Co., The Chas. H., New York, N. Y.....	47
Sanborn Company, Cambridge, Mass.....	46
Sandoz Chemical Works, Inc., New York, N. Y.....	10
Saunders Company, W. B., Philadelphia, Pa.....	54
Schering Corporation, Bloomfield, N. J.....	26
Searle & Co., G. D., Chicago, Ill.....	6
Squibb & Sons, E. R., New York, N. Y.....	49
Stearns & Company, Frederick, Detroit, Mich.....	11
Sun-A-Sured, Inc., Chicago, Ill.....	24
Upsher Smith Company, Minneapolis, Minn.....	15
Wander Co., The, Chicago, Ill.....	59
Winthrop Chemical Company, Inc., New York, N. Y.....	41

CHICAGO PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

A program of special features has been arranged, but ample time has been allowed for sight-seeing, shopping and recreation. Complete lists of museums, principal shops, current public lectures, concerts, and theaters will be issued by the local committee.

MONDAY, APRIL 16, 1934

Morning: Registration at the Palmer House—9 a.m. to 5 p.m.

Suggestions: The Art Institute, The Field Museum of Natural History, The Adler Planetarium, and the Shedd Aquarium.

TUESDAY, APRIL 17, 1934

Morning: Registration at the Palmer House—9 a.m. to 5 p.m.

Afternoon: The visiting women will be the guests of the local committee at a reception and luncheon at the Casino Club, 195 East Delaware Place, at twelve-thirty.

This makes a convenient starting point for visits to the Alexander McKimlock Campus of Northwestern University, to Lincoln Park in which are located the Museum of the Chicago Academy of Sciences, the famous St. Gauden's statue of Lincoln, the beautiful new building of the Chicago Historical Society and other points of interest. The drive along Lake Michigan through Lincoln Park over newly made land to Foster Avenue and return is most attractive and affords one of the finest views of Chicago's sky line. The Casino Club is a block east of upper Michigan Avenue which is famous for its shops.

WEDNESDAY, APRIL 18, 1934

Afternoon: The members of the local committee invite the visiting women to a tea at the Arts Club, 410 North Michigan Avenue (Wrigley Building North) from four-thirty to six.

Evening: The Convocation of the College is held in the Grand Ballroom of the Palmer House at eight o'clock. The women are invited to attend.

THURSDAY, APRIL 19, 1934

Morning: 10:00 o'clock. Special busses will leave the Palmer House for the University of Chicago Campus where visits will be made to the Oriental Institute and the International House. Those who wish to visit the Museum of Science and Industry located in the Fine Arts Building of the 1893 World's Fair which has been reconstructed in marble, may obtain luncheon at the International House.

Evening: 7:30 o'clock. The Annual Banquet of the College at the Palmer House.

GENERAL SESSIONS

The membership of the American College of Physicians is composed of internists who represent every branch and subdivision of internal medicine. This fact has been borne in mind in the preparation of the program for the General Sessions. An effort has been made to present timely subjects that will prove not only of interest to medical men in general, but will also be of definite value to those engaged in the more special fields of medicine. The speakers, who come from various parts of this country and Canada, have been selected because of their fitness to speak with authority upon the subjects in which they are particularly interested. We have endeavored to stress on this program topics in which widespread interest has developed or in which definite advances have been made recently. The limited time available for the General Sessions has made it obviously impossible to include all the subjects of importance to the internist, but it is earnestly hoped that the choice that has been made will furnish a program that will prove both interesting and profitable.

Special attention should be called to certain features of the program.

Cardiovascular Disease which is constantly attaining increased importance in our modern civilization will accordingly be especially emphasized. A number of papers will be found devoted to various practical considerations of this subject. Notable among these are the contributions on coronary occlusion, a discussion of the most recent observations on the etiology of arterial hypertension, and papers dealing with

the rôle of total ablation of the thyroid in angina pectoris and congestive heart failure and the use of a new drug in cardiovascular disease. Great interest has been shown of late in the diagnosis and treatment of peripheral vascular disease. This subject will be discussed by one of the outstanding workers in this field.

Infectious Diseases have been accorded definite consideration. Among the important topics to be discussed are a recent encephalitis epidemic, certain virus diseases transmissible to man, undulant fever, the permanent nature of various acute infections, and the latest advance in the treatment of lobar pneumonia; namely, therapeutic pneumothorax.

Metabolic Diseases have not been neglected. Certain aspects of diabetes will be considered, as well as subjects of such wide physiological and clinical interest as energy exchange in disease and alkalosis.

Nervous Diseases will be discussed chiefly from the viewpoint of the internist. The psychological approach to the patient will be stressed, as well as certain problems in organic neurology and fever therapy.

Hematology—Although, because of its recent and admirable presentation before the College, the subject of pernicious anemia will not be discussed, other important aspects of diseases of the blood will be considered. There will be an essay on the broad subject of development in blood studies. Various aspects of granulopenia, newer conceptions of the monocyte, and the practical value of blood sedimentation tests will be considered.

Gastro-enterology will be covered from certain special angles. The recent advances in the physiology of the liver and biliary tract and the value of estimating the functional capacity of the liver will be emphasized. Various intestinal conditions and their management, as well as the relationship between gastrointestinal and other visceral diseases, will be considered.

Tuberculosis will be given adequate consideration, especially from the standpoint of its medical and surgical treatment. There will be a paper on the newer conception of hematogenous pulmonary tuberculosis, as well as one on cutaneous tuberculosis.

Pulmonary Diseases will be discussed from the standpoint of the bronchoscopist, and special topics such as lung abscess and bronchomoniliasis will also be discussed.

Pediatrics—An effort has been made to have a number of outstanding contributions presented dealing with some of the broad problems that are engaging the attention of those who are particularly interested in internal medicine as it applies to children.

A number of other important but unrelated subjects will be discussed during the General Sessions. For example, papers will be presented on the relationship of allergic diseases to internal medicine, as well as on the new group of drugs known as metabolic stimulants; diaphragmatic hernia; studies on the etiology of cancer; physical therapy; certain aspects of rheumatoid arthritis, and other papers of equal importance.

Endocrinology, which was so completely covered at the last meeting of the College, will not have a prominent part in the program this year.

The much discussed topic of *national health insurance* will be the subject of an address by a distinguished speaker who is unusually well qualified to discuss this timely problem.

It has been possible to construct a program such as the one above outlined, which we trust will prove a well-balanced grouping of papers on subjects of outstanding importance, because of the hearty coöperation and ready response of the Fellows of the College and the others who were invited to participate in the General Sessions. To all of them are due our sincere thanks.

GENERAL SESSIONS

Chicago, Ill.—April 16–20, 1934

OPENING GENERAL SESSION

Monday Afternoon, April 16, 1934

2:00 o'Clock

GRAND BALLROOM, PALMER HOUSE.

1. Addresses of Welcome:

James B. Herrick, General Chairman of the Eighteenth Annual Clinical Session.

Austin A. Hayden, President of the Chicago Medical Society.

Irving S. Cutter, On Behalf of the Chicago Medical Schools.

2. Response to Addresses of Welcome:

George Morris Piersol, President of the American College of Physicians.

3. Arteriolar Infarction.

Jonathan C. Meakins, Montreal, Que.

4. Malaria Therapy in Asymptomatic Neurosyphilis.

Paul A. O'Leary, Rochester, Minn.

5. Bronchoscopy in Pulmonary Disease: Its Present Status as an Aid in Diagnosis and Treatment.

Gabriel Tucker, Philadelphia, Pa.

6. Diaphragmatic Hernia.

Carl A. Hedblom, Chicago, Ill.

7. Observations on the Diagnosis and Treatment of Peripheral Vascular Disease.

Eugene M. Landis, Philadelphia, Pa.

8. Hepatic Function in Relation to Hepatic Pathology.

Frank C. Mann, Rochester, Minn.

SECOND GENERAL SESSION

Monday Evening, April 16, 1934

8:00 o'Clock

GRAND BALLROOM, PALMER HOUSE

Presiding Officer

James Alex. Miller, New York, N. Y.

1. Development and Disappointments in Blood Studies.

Roger I. Lee, Boston, Mass.

2. The Tuberculosis of Childhood.

Charles Hendee Smith, New York, N. Y.

3. The Permanent Nature of Various Common Infections.

Allen K. Krause, Tucson, Ariz.

4. Therapeutic Pneumothorax in Experimental Lobar Pneumonia in Dogs.

Simon S. Leopold, Philadelphia, Pa.

5. Virus Diseases of Animals Transmissible to Man.
Karl F. Meyer, San Francisco, Calif.

10:20 o'Clock

SMOKER

Red Lacquer Room, Palmer House

An unusual program of entertainment, both amusing and instructive, has been arranged.

THIRD GENERAL SESSION

Tuesday Afternoon, April 17, 1934

2:00 o'Clock

GRAND BALLROOM, PALMER HOUSE

Presiding Officer

Ernest B. Bradley, Lexington, Ky.

1. Energy Exchange in the Study and Management of Disease.
L. H. Newburgh, Ann Arbor, Mich.
2. Leukopenia in Tuberculosis with Report of a Case Showing a Complete Neutropenic Episode for One Week,—Recovery.
Charles H. Cocke, Asheville, N. C.
3. Newer Clinicopathologic Considerations of the Monocyte and of Monocytic Leukosis.
Charles A. Doan and Bruce K. Wiseman, Columbus, Ohio.
4. The Diagnosis and Management of Certain Types of Chronic Diarrhea.
Philip W. Brown, Rochester, Minn.
5. Small Intestinal Intubation: Experiences with a Double-Lumened Tube.
T. Grier Miller and W. Osler Abbott, Philadelphia, Pa.
6. The Criteria of Alcohol Intoxication with Special Reference to 3.2 Beer.
A. J. Carlson, Chicago, Ill.

INTERMISSION

7. Proliferative and Exudative Tuberculosis in Their Relationship to the Various Fractions of ⁱⁿ Tubercle Bacillus.
Francis M. Potter, Monrovia, Calif.
8. Metabolic Stimulants (^{spe} lium Dinitrophenol).
Edward L. Bortz, Philadelphia, Pa.
9. Surgical Treatment of ^{co} ulmonary Tuberculosis.
Ralph C. Matson, Portland, Ore.
10. Allergic Diseases in ^g eneral Practice.
Harry B. Wilms, and Merle Miller, Philadelphia, Pa.
11. Institutional Treatment for the Chronic Invalid and Convalescent.
Elmer L. Eggleston, Battle Creek, Mich.

FOURTH GENERAL SESSION

Tuesday Evening, April 17, 1934

8:00 o'Clock

GRAND BALLROOM, PALMER HOUSE

Presiding Officer
Arthur R. Elliott, Chicago, Ill.

1. The Encephalitis Epidemic in St. Louis.
David P. Barr, St. Louis, Mo.
2. Results of Further Studies on the Physiology of the Anterior Pituitary.
J. B. Collip, Montreal, Que.
3. Treatment of Angina Pectoris and Congestive Heart Failure by Total Ablation of the Thyroid in Patients without Thyrotoxicosis.
Herrman L. Blumgart, Boston, Mass.
4. Studies of Cell Potencies and Some Relations to Neoplasia.
Stanley P. Reimann, Philadelphia.
5. Biliary Dyskinesia.
A. C. Ivy, Chicago, Ill.
6. Hematogenous Pulmonary Tuberculosis.
James Alex. Miller, New York, N. Y.

FIFTH GENERAL SESSION

Wednesday Afternoon, April 18, 1934

2:00 o'Clock

GRAND BALLROOM, PALMER HOUSE

Presiding Officer
James G. Carr, Chicago, Ill.

1. The Recent Trend Towards a Differentiation between Allergy and Immunology, and the Relationship to Clinical Medicine.
Lay Martin, Baltimore, Md.
2. An Explanation of the Mechanism of Infantile Paralysis Production in the Human.
John A. Toomey, Cleveland, Ohio.
3. A Critical Discussion of the Etiological Factors in Arterial Hypertension.
Soma Weiss, Boston, Mass.
4. Remarks on the Diagnosis of Coronary Occlusion.
Louis Hamman, Baltimore, Md.
5. Cutaneous Tuberculosis and Its Relationship to General Medicine.
Francis E. Senear, Chicago, Ill.

INTERMISSION

6. The Blood Sedimentation Test: The Value of Its Use as a Routine, Especially in Pulmonary Tuberculosis.
Paul H. Ringer, Asheville, N. C.

7. Glycogen Formation in Diabetes.
F. D. W. Lukens, Philadelphia, Pa.
8. Trends in Diet in Diabetes.
R. T. Woodyatt, Chicago, Ill.
9. The Diabetic Child.
Henry J. John, Cleveland, Ohio.
10. Alkalosis: A Clinical Problem.
Charles T. Way and Edward Muntwyler, Cleveland, Ohio.
11. Certain Bases of Physical Therapy.
Thomas P. Sprunt, Baltimore, Md.
12. Acquired Heart Block with Adams-Stokes Attacks Dependent upon a Congenital Anomaly (Persistent Ostium Primum): Report of a Case.
Wallace M. Yater, Washington, D. C., Chas. W. Barrier, Fort Worth, Tex.,
and Paul E. McNabb, Washington, D. C.

ANNUAL CONVOCATION

Wednesday Evening, April 18, 1934

8:00 o'clock

GRAND BALLROOM, PALMER HOUSE

The general profession and the general public are cordially invited. No special admission tickets are required.

1. Convocation Ceremony.
2. Address: "The Medical Aspects of National Health Insurance."
Grant Fleming, Director of the Department of Public Health and Preventive Medicine, McGill University, Montreal, Que.
3. Presidential Address.
George Morris Piersol, Philadelphia, Pa.

Presidential Reception

RED LACQUER ROOM

The Reception will follow immediately after the program. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the interim between the Convocation and the Reception.

Dancing

SIXTH GENERAL SESSION

Thursday Afternoon, April 19, 1934

2:00 o'clock

GRAND BALLROOM, PALMER HOUSE

Presiding Officer

Jonathan C. Meakins, Montreal, Que.

1. Further Studies on Granulopenia with Report of Fifteen Additional Cases.
Stewart R. Roberts and Roy R. Kracke, Atlanta, Ga.

2. Non-Painful Features of Coronary Occlusion.
S. Marx White, Minneapolis, Minn.
3. Classification of Vascular Disease with Special Reference to Etiology, Pathological Anatomy and Pathological Physiology.
Nathan S. Davis, III, Chicago, Ill.
4. Blood Pressure Variations as a Guide to Treatment and Prognosis.
Clarence L. Andrews, Atlantic City, N. J.
5. The Early Recognition of Myocardial Disease.
Walter L. Bierring, Des Moines, Iowa.
6. The Use of Verodigen (a Digitalis Glucoside) in Cardiovascular Disease: Its Pharmacological Assay and Effects on Animals.
W. D. Stroud, A. E. Livingston, A. W. Bromer, J. B. Vander Veer and G. C. Griffith, Philadelphia, Pa.

INTERMISSION

7. Cardiovascular Observations in 215 Neurosyphilitics.
Clough T. Burnett and Charles A. Rymer, Denver, Colo.
8. Influential Factors in Recovery from Rheumatoid Arthritis.
Russell L. Cecil, New York, N. Y.
9. Creatine Metabolism and Blood Cholesterol as Aids in the Diagnosis and Treatment of Hypothyroidism in Children.
Julius H. Hess, Chicago, Ill.

The Annual General Business Meeting of the College will be held in the *Red Lacquer Room* immediately after the last paper. All Masters and Fellows are urged to attend. Official reports from the Executive Secretary and Treasurer will be read; new Officers, Regents and Governors will be elected, and the President-Elect, Dr. Jonathan C. Meakins, will be inducted into office.

Thursday Evening, 8:00 o'Clock

GRAND BALLROOM, PALMER HOUSE

THE ANNUAL BANQUET OF THE COLLEGE

(Procure Tickets at the Registration Bureau)

Toastmaster: James B. Herrick, Chicago, Ill.

Address: "The Renewal of America."

Dr. Glenn Frank, President of the University of Wisconsin.

FINAL GENERAL SESSION

Friday Afternoon, April 20, 1934

2:00 o'Clock

GRAND BALLROOM, PALMER HOUSE

Presiding Officer

James H. Means, Boston, Mass.

1. The United States Pharmacopoeia XI. Its Relation to Internal Medicine and the Scientific Nature of Its Revision.
Virgil E. Simpson, Louisville, Ky.

2. The Treatment of Lung Abscess.
Frederick T. Lord, Boston, Mass.
3. Evaluation of Methods for Testing the Functional Capacity of the Liver.
William J. Kerr, San Francisco, Calif.
4. Abdominal Pain: Its Significance and Diagnostic Value.
Thomas R. Brown, Baltimore, Md.
5. Diseases of the Nervous System Producing Dysfunction of other Organs, and
Dysfunction of other Organs Producing or Simulating Diseases of
the Nervous System.
Lewis J. Pollock, Chicago, Ill.
6. The Thymus and Status Thymico-Lymphaticus.
A. Graeme Mitchell, Cincinnati, Ohio.

INTERMISSION

7. Undulant Fever.
Joseph L. Miller, Chicago, Ill.
8. Personality Study in the Practice of Internal Medicine.
Edward Weiss, Philadelphia, Pa.
9. A Study of Ten Cases of Bronchomoniliasis.
John W. Flinn, Robert S. Flinn and Zebud M. Flinn, Prescott, Ariz.
10. Factors Influencing Operative Mortality in Hyperthyroidism.
Willard O. Thompson, S. G. Taylor, III, and Karl A. Meyer, Chicago, Ill.
11. The Interrelationship of Renal and Gastrointestinal Disease.
Harry Gauss, Denver, Colo.

THE CLINIC PROGRAM

An effort has been made in preparing the program to render available what is most interesting in medicine that Chicago has to offer. The laboratories and clinical centers of the Universities have been enlisted to display the best they have in research and clinic, while the Cook County Graduate School of Medicine, in affiliation with Cook County Hospital, will furnish unusual facilities to survey the work being done in that great hospital.

A special effort has been made to include in the program a larger contribution from Pediatrics than is usual. Roentgenology has been drawn upon heavily and interesting demonstrations in tuberculosis have been arranged for. Clinico-pathologic conferences, symposia on endocrinology, cardiovascular problems, neurology, and hematology, besides mixed clinics of varied interest, will be given in the principal hospitals.

Convenience of access has been kept in view and the geographic area covered is sufficiently circumscribed to avoid waste of time in getting from one center to another.

Clinics and demonstrations will be held in the forenoons from 9:00 to 12:00 daily, Tuesday to Friday, inclusive.

Tickets will be required for each and every one of the special clinics, ward rounds and demonstrations. The coöperation of every one in securing his clinic tickets will assist greatly in distributing the attendance according to the capacity of each program. It is self-evident that a ward round arranged for twenty-five will lose its value for all if forty or fifty are present. Ticket registration naturally is the only effective method of keeping the attendance within the capacities indicated.

Tuesday, April 17, 1934

A-1 UNIVERSITY OF CHICAGO—ALBERT MERRITT
BILLINGS HOSPITAL
(950 E. 59th Street)

Room P 117

(Capacity—256)

- 9:00– 9:20 Experimental Studies on the Etiology of Peptic Ulcer.
 Warren B. Matthews.
- 9:20– 9:40 The Relative Importance of Acid and of Pepsin in the Etiology of
 Ulcer.
 Lester R. Dragstedt.
- 9:40–10:00 The Treatment of Peptic Ulcer.
 Walter L. Palmer.
- 10:00–10:45 The Relationship of Circulating Antipneumococcal Immune Substances
 to the Course of Lobar Pneumonia.
 O. H. Robertson, J. B. Graeser and L. T. Coggeshall.
- 10:45–11:30 The Diagnosis of Early Pulmonary Tuberculosis.
 Robert G. Bloch.
- 11:30–12:00 Experimental Poliomyelitis.
 N. Paul Hudson.

A-2 UNIVERSITY OF CHICAGO—ALBERT MERRITT
BILLINGS HOSPITAL
(950 E. 59th Street)

Room M 137

(Capacity—85)

- 9:00– 9:30 Motion Pictures of Experimental Increased Intracranial Pressure.
 Arno B. Luckhardt.
- 9:30–10:00 Clinical Aspects of Increased Intracranial Pressure.
 Paul C. Bucy.
- 10:00–10:30 Peculiarities of Intracranial Tumors in Childhood.
 Percival Bailey.
- 10:30–11:15 Some Recent Observations on the Physiology of Sleep.
 Nathaniel Kleitman.
- 11:15–11:30. Pain.
 Arno B. Luckhardt.
- 11:30–12:00 Studies on the Physiology of the Bladder with Operative Relief of
 Vesical Paralysis.
 Douglas N. Buchanan and Charles B. Huggins.

A-3 UNIVERSITY OF CHICAGO—ALBERT MERRITT
BILLINGS HOSPITAL
(950 E. 59th Street)

Room M 433

(Capacity—25)

- 9:00–10:30 Bedside Clinic on Cardiac and Renal Vascular Diseases.
 Louis Leiter and Emmet B. Bay.

A-4 UNIVERSITY OF CHICAGO—ALBERT MERRITT
BILLINGS HOSPITAL
(950 E. 59th Street)

Outside of Room P 118

(No set capacity)

- 9:00-12:00 The Rôle of X-Ray in the Clinical Study of Heart Disease—Exhibition of Films.
Paul C. Hodges.
-

B CHILDREN'S MEMORIAL HOSPITAL
(700 Fullerton Avenue)

Auditorium, Nurses' Home

(Capacity—250)

Dr. Brennemann will discuss each subject briefly by way of introduction. The main presentation will be of x-ray lantern slides.

- 9:00-10:00 Empyema in Children with Special Emphasis on the Rôle of Aspiration in Treatment.
E. T. McEnery.
- 10:00-11:00 X-Ray Diagnosis of Intrathoracic Tuberculosis in Children.
J. A. Bigler.
- 11:00-12:00 The Interrelationship of Collapsed Lung, the Triangular X-Ray Lung Shadow and Bronchiectasis.
W. E. Anspach.
-

C-1 COOK COUNTY GRADUATE SCHOOL OF MEDICINE
(In affiliation with the Cook County Hospital)
COOK COUNTY HOSPITAL
(West Harrison and South Wood Streets)

Medical Amphitheatre

(Capacity—150)

- 9:00- 9:45 Amebiasis and Its Therapy.
Sidney A. Portis.
- 9:45-10:30 Gastric and Duodenal Ulcer.
Jacob Meyer.
- 10:30-11:15 Diabetes and Cardiovascular Disease.
William J. Quigley.
- 11:15-12:00 Atypical Types of Perforated Peptic Ulcer.
Harry Singer.
-

C-2 COOK COUNTY GRADUATE SCHOOL OF MEDICINE
(West Harrison and South Wood Streets)

Surgical Amphitheatre

(Capacity—150)

- 9:00-9:45 Pulmonary Heart Disease.
Harry J. Isaacs.

- 9:45-10:30 Rheumatic Diseases.
Isadore Pilot.
- 10:30-11:15 Pituitary Disorders.
Frank B. Lusk.
- 11:15-12:00 Presentation of Heart Cases.
Laurence E. Hines.
-

C-3 COOK COUNTY GRADUATE SCHOOL OF MEDICINE
(West Harrison and South Wood Streets)

Amphitheatre—Children's Building

(Capacity—100)

- 9:00- 9:45 Rheumatic Heart Disease in Children.
Philip Rosenblum.
- 9:45-10:30 Tremor in Newly Born.
Maxwell P. Borovsky.
- 10:30-11:15 Pulmonary Disease in Children.
Maurice L. Blatt.
- 11:15-12:00 Diagnosis and Treatment of Gonorrheal Vaginitis.
Maurice Schneider.
-

C-4 COOK COUNTY GRADUATE SCHOOL OF MEDICINE
(West Harrison and South Wood Streets)

Bedside Clinics

(Capacity—15)

- C-4a 9:00-11:00 Ward 64.
Harry J. Isaacs.
- C-4b 10:00-12:00 Ward 54.
Jacob Meyer.
- C-4c 10:30-12:00 Ward 64.
Italo F. Volini.
- C-4d 11:00-12:00 Ward 61.
Frederick Tice.
-

D UNIVERSITY OF ILLINOIS
(1817 W. Polk Street)

Room 106

(Capacity—200)

R. W. Keeton presiding

- 9:00- 9:20 The Clinical Differentiation of Medical and Surgical Jaundice.
Edmund F. Foley.
- 9:20- 9:40 Syphilis of the Stomach.
Harry A. Singer.
- 9:40-10:00 The Management of Ulcerating Diseases of the Colon.
Michael H. Streicher.
- 10:00-10:20 The Physiology of the Failing Heart.
M. B. Visscher.

- 10:20-10:40 Long Standing Valvular Disease: Onset of Auricular Fibrillation without Effect upon Benign Course of the Disease.
Sidney Strauss.
- 10:40-11:00 Neuro-circulatory Asthenia: An Attempt to Analyze the Mechanism Involved.
Ford K. Hick.
- 11:00-11:20 The Differentiation of Hemophilia from Purpura Hemorrhagica and Other Hemorrhagic Disease with Blood. (Lantern slide demonstration.)
Carroll L. Birch.
- 11:20-11:40 Dental Extractions in Hemophiliacs.
Walter W. Dalitsch.
- 11:40-12:00 Arthritis Classification and Therapy with Particular Reference to the Use of Vaccine.
Isadore Pilot.
-

E LOYOLA UNIVERSITY and MERCY HOSPITAL
(2537 Prairie Avenue)

Amphitheatre
(Capacity—350)

- 9:00-10:00 Endocrine Clinic.
A. W. Schram.
- 10:00-11:00 Gastrointestinal Clinic.
Fred M. Drennan.
- 11:00-12:00 Cardiorenal Clinic.
Milton Mandel.
-

F-1 MICHAEL REESE HOSPITAL
(29th Street and Ellis Avenue)

Sarah Morris Amphitheatre, 2901 Ellis Avenue

(Capacity—170)

Gallbladder Study Group

- 9:00- 9:15 Discussion of Recent Investigative Work in Gallbladder Disease.
Leon Bloch.
- 9:15- 9:30 Preoperative and Postoperative Medical Care of Gallbladder Patients.
Sidney A. Portis.
- 9:30- 9:40 Bromsulphonphthalein Liver Function Test: Crystallography as Aid in Diagnosis of Lithiasis.
A. Serby.
- 9:40- 9:50 The Galactose and Urobilinogen Tests in the Differential Diagnosis of Jaundice.
D. Rosenberg.
- 9:50-10:00 Electrocardiographic Tracings During Manipulations of Gallbladder at Operation.
L. Katz.
- 10:00-10:10 The Liver in Gallbladder Disease.
S. Soskin.
- 10:10-10:20 Correlation of X-Ray and Pathological Findings in a Series of Patients Operated Upon for Gallbladder Disease.
G. Lichtenstein.

- 10:20-10:40 Gallbladder Disease and Surgery. A Report of Methods of Diagnosis, Treatment and Especially Results.
Ralph B. Bettman.
- 10:40-11:00 Discussion: To be opened by
G. B. Eusterman, Mayo Clinic, Rochester, Minn.

MICHAEL REESE HOSPITAL
(29th Street and Ellis Avenue)

Rothschild Amphitheatre, 2816 Ellis Avenue
(Capacity—330)

Heart Study Group

F-2a *A. Recent Studies of Coronary Diseases*

- 9:00- 9:10 Anatomical Observations.
Otto Saphir.
- 9:10- 9:20 Mechanism of Pain Production.
Louis N. Katz.
- 9:20- 9:30 The Electrocardiographic Diagnosis.
L. N. Katz, A. Bohning and H. Landt.
- 9:30- 9:40 Clinical Observations.
Walter W. Hamburger.

F-2b *B. The Thyroid and Heart Disease*

- 9:50-10:00 Heart in Hyperthyroid Disease.
William Buchbinder.
- 10:00-10:10 Masked Hyperthyroidism.
Morris W. Lev.
- 10:10-10:20 Dynamics of Heart Failure.
Louis N. Katz.
- 10:20-11:00 Total Ablation of the Thyroid as a Treatment of Congestive Heart Failure and of Angina Pectoris.
H. Blumgart, Beth Israel Hospital and Harvard University, Boston, Mass.

F-3 MICHAEL REESE HOSPITAL
(29th Street and Ellis Avenue)

Classroom of the Nurses' Home, 2816 Ellis Avenue
(Capacity—60)

- 11:00-12:00 Uses and Limitations of Encephalography.
A. Levinson.

G MUNICIPAL TUBERCULOSIS SANITARIUM
(5601 N. Crawford Avenue, at Bryn Mawr Avenue)

Morgue, in the Laboratory Building
(Capacity—50)

- 10:00-12:00 Pathological-Clinical Conference.
Autopsy demonstrations.

Demonstration of specimens in museum.
 Slide specimens and gross pathology.
 Antemortem and postmortem x-ray plate demonstrations, in connection with pathological specimens shown.
 Henry C. Sweany.

H-1 NORTHWESTERN UNIVERSITY MEDICAL SCHOOL
 (303 East Chicago Avenue)

Room 541

(Capacity—125)

- 9:10- 9:40 Orthopedic and Medical Management of Chronic Infectious Arthritis:
 Demonstration of Patients.
 Emil Hauser.
- 9:40-10:10 (a) Cases of Chronic Infectious Arthritis Treated by Hyperpyrexia:
 A Review of Results.
 (b) Knee-joint Visualization: Its Value in the Differential Diagnosis
 of Conditions Simulating Arthritis.
 David E. Markson.
- 10:10-10:40 Medical Management of Chronic Obstructive Peptic Ulcer with Pres-
 entation of Cases.
 Lowell D. Snorf.
- 10:40-11:10 Bronchiectasis: Demonstration of Cases.
 Jerome R. Head.
- 11:10-11:30 Amebiasis.
 A. A. Goldsmith.
- 11:30-12:00 Laboratory Diagnosis of *Entameba Histolytica*, with Microscopic
 Moving Picture.
 Fred O. Tonney.
-

H-2 NORTHWESTERN UNIVERSITY MEDICAL SCHOOL
 (303 East Chicago Avenue)

Room 393

(Capacity—20)

- 10:00-11:00 Physical Therapy in Arthritis: Demonstration of a Program for Home
 and Office Treatment.
 John S. Coulter.
- 11:00-12:00 Demonstration of Capillary Changes Following Physiotherapeutic
 Measures.
 Gilbert H. Marquardt.
-

H-3 PASSAVANT MEMORIAL HOSPITAL
 (303 East Superior Street)

Room 108

(Capacity—25)

- 10:30-12:00 Oxygen Therapy: Demonstration of Oxygen Chamber, Tent and Ca-
 theter Technic.
 M. H. Barker.

I-1 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL
(1753 West Congress Street)

North Amphitheatre

(Capacity—75)

- 9:00– 9:30 Rôle of the Kidney in the Acid Base Balance of the Body.
Howard M. Sheaff.
9:30–10:30 Present Concepts of Bright's Disease.
Wilber E. Post.
10:30–11:30 Abdominal Enlargements in Children with Special Reference to the
Spleen and Liver.
Clifford G. Grulee.
11:30–12:00 Behavior Clinic.
Harry R. Hoffman.
-

I-2 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL
(1753 West Congress Street)

South Amphitheatre

(Capacity—100)

- 9:30–10:00 Some Features of the Diagnosis of Amebic Dysentery.
Alva A. Knight.
10:00–11:00 Diarrheas.
Donald P. Abbott.
11:00–11:30 Toxic Effects from Alkalies in Ulcer Management.
L. C. Gatewood.
11:30–12:00 Pituitary Basophilism.
A. R. Colwell.
-

J ST. LUKE'S HOSPITAL
(1437 South Michigan Avenue)

Nurses' Hall—2d Floor

(Capacity—250)

- 9:00– 9:30 Chronic Rheumatism of the Spine.
Joseph L. Miller.
9:30–10:30 (a) Surgical Treatment of Pulmonary Tuberculosis.
(b) Treatment of Bronchiectasis.
(c) Pulmonary Abscess.
Carl A. Hedblom.
10:30–11:00 Studies of the Peripheral Circulation.
Carl Johnson and George Scupham.
11:00–12:00 The Value of Malaria Therapy in Asymptomatic Neurosyphilis.
Paul O'Leary, Rochester, Minn.

Wednesday, April 18, 1934

A-1 UNIVERSITY OF CHICAGO—ALBERT MERRITT
BILLINGS HOSPITAL
(950 E. 59th Street)

Room P 117

(Capacity—256)

- 9:00– 9:30 A Case of Thickened Pericardium with Partial Pericardiectomy and
the Clinical Syndrome of Portal Obstruction.
Louis Leiter and Dallas B. Phemister.
- 9:30–10:00 The Case Against the Nitrites in Angina Pectoris.
Emmet B. Bay.
- 10:00–10:45 Pain in Heart Disease.
Joseph A. Capps.
- 10:45–11:00 Heart Disease in Pregnancy.
Knute A. Reuterskiold.
- 11:00–12:00 Clinic on Heart Disease.
Alfred Stengel, Philadelphia, Pa.

A-2 UNIVERSITY OF CHICAGO—ALBERT MERRITT
BILLINGS HOSPITAL
(950 E. 59th Street)

Room M 137

(Capacity—85)

- 9:00– 9:30 Clinic on Allergy.
Harry L. Huber.
- 9:30–10:00 Vasomotor Rhinitis.
Theodore E. Walsh.
- 10:00–10:30 Significance of Abnormal Variations in Acid-Base Balance.
A. B. Hastings.
- 10:30–11:00 A Discussion of Renal Function.
Henry L. Schmitz.
- 11:00–11:30 Renal Function Tests in Pregnancy.
William J. Dieckmann.
- 11:30–11:50 The Acid-Base Balance in Fatigue.
Frederic W. Schlutz.

A-3 UNIVERSITY OF CHICAGO—ALBERT MERRITT
BILLINGS HOSPITAL
(950 E. 59th Street)

Outside of Room P 118

(No Set Capacity)

- 9:00–12:00 The Rôle of X-Ray in the Clinical Study of Heart Disease: Exhibi-
tion of Films.
Paul C. Hodges.

B CHILDREN'S MEMORIAL HOSPITAL
(700 Fullerton Avenue)

Auditorium Nurses' Home

(Capacity—250)

- 9:00–10:00 Blood Disorders in Children.
Mila Pierce.
10:00–11:00 Cardiac Disease in Childhood.
Stanley Gibson.
11:00–12:00 Nephritis in Children.
C. A. Aldrich.
-

C-1 COOK COUNTY GRADUATE SCHOOL OF MEDICINE
(In affiliation with the Cook County Hospital)
COOK COUNTY HOSPITAL
(West Harrison and South Wood Streets)

Medical Amphitheatre

(Capacity—150)

- 9:00– 9:45 Primary Carcinoma of the Lung, Clinical and X-Ray.
Aaron Arkin:
9:45–10:30 Chronic Lead Intoxication.
George W. Scupham.
10:30–11:15 Pericarditis.
Isadore N. Trace.
11:15–12:00 Verodigen (Digitalis) in Treatment of Heart Disease.
Italo F. Volini.
-

C-2 COOK COUNTY GRADUATE SCHOOL OF MEDICINE
COOK COUNTY HOSPITAL
(West Harrison and South Wood Streets)

Surgical Amphitheatre

(Capacity—150)

- 9:00– 9:45 Pneumothorax.
Jacob J. Mendelsohn.
9:45–10:30 Polycythemia Vera: Chronic Hemolytic Icterus.
LeRoy H. Sloan.
10:30–11:15 Asthma and Asthmatoïd Conditions.
Samuel M. Feinberg.
11:15–12:00 Chronic Arthritis: Bacteriologic Aspects.
Eugene F. Traut.
-

C-3 COOK COUNTY GRADUATE SCHOOL OF MEDICINE
COOK COUNTY HOSPITAL
(West Harrison and South Wood Streets)

Amphitheatre, Children's Building

(Capacity—100)

- 9:00– 9:45 Endocrine Disturbances in Children.
Charles Stulik.

- 9:45-10:30 Nephritis.
Joseph K. Calvin.
- 10:30-11:15 Surgical Treatment of Tuberculosis in Childhood.
Joseph Greengard.
- 11:15-12:00 The Care of the Newly Born.
Craig Butler.

C-4 COOK COUNTY GRADUATE SCHOOL OF MEDICINE
COOK COUNTY HOSPITAL
(West Harrison and South Wood Streets)

Bedside Clinics

(Capacity—15)

- C-4a 9:00-12:00 Ward 65.
Aaron Arkin.
- C-4b 9:00-12:00 Ward 64.
William J. Quigley.
- C-4c 9:30-12:00 Ward 35.
George W. Scupham.
- C-4d 10:00-12:00 Ward 45.
Samuel M. Feinberg.
- C-4e 10:00-12:00 Ward 25.
Laurence E. Hines.
- C-4f 10:00-12:00 Ward 63.
Sidney A. Portis.
- C-4g 10:00-12:00 Ward 63.
Isadore N. Trace.
- C-4h 10:00-12:00 Ward 60.
Leon Unger.
- C-4i 11:00-12:00 Ward 15.
Clarence J. McMullen.
- C-4j 11:00-12:00 Ward 61.
Frederick Tice.

D

UNIVERSITY OF ILLINOIS
(1817 W. Polk Street)

Room 106

(Capacity—200)

Frederick H. Falls and H. Douglas Singer Presiding

- 9:00- 9:20 The Use of Immune Serum in Puerperal Sepsis.
Abraham F. Lash.
- 9:20- 9:40 The Treatment of Menstrual Disorders by the Injection of Extracts of
Anterior Pituitary Hormone.
William H. Browne.
- 9:40-10:00 Studies in Obesity with Presentation of Cases.
Robert W. Keeton.
- 10:00-10:20 Eclampsogenic Toxemia.
Frederick H. Falls.
- 10:20-10:40 The Tonic Pupil.
George B. Hassin.

- 10:40-11:00 Tumors of the Cord.
Eric Oldberg.
- 11:00-11:20 Psychiatry in General Practice.
H. Douglas Singer.
- 11:20-11:40 Contributions of the Oculist to Neurological Diagnosis.
Hallard Beard.
- 11:40-12:00 Speech after Laryngectomy with Case Demonstration.
Francis L. Lederer.

E LOYOLA UNIVERSITY and MERCY HOSPITAL
(2537 Prairie Avenue)

Amphitheatre

(Capacity—350)

- 9:00-10:00 General Medicine.
Walter G. McGuire.
- 10:00-11:00 Clinical Interpretation of Pain and Tenderness in the Abdominal Wall.
Peter T. Bohan, Kansas City, Mo.
- 11:00-12:00 Cardiac Clinic.
Robert S. Berghoff.

F-1 MICHAEL REESE HOSPITAL
(29th Street and Ellis Avenue)

Sarah Morris Amphitheatre, 2901 Ellis Avenue

(Capacity—170)

Metabolism and Endocrine Glands

- 9:00- 9:15 Influencing Metabolism by Surgical Methods.
L. Zimmerman.
- 9:20- 9:35 The Functions of the Hypophysis.
W. Saphir.
- 9:40- 9:55 Nephrosis.
Joseph K. Calvin.
- 10:00-10:15 Cholesterol Metabolism.
A. Mirsky.
- 10:20-10:35 Carbohydrate Disturbance in Hyperthyroidism.
S. Soskin.
- 10:40-11:00 Obesity.
Solomon Strouse.

F-2 MICHAEL REESE HOSPITAL
(29th Street and Ellis Avenue)

Rothschild Amphitheatre, 2816 Ellis Avenue

(Capacity—330)

Tumor Clinic

- 9:00- 9:45 Indications, Limitations and Advances in the Radium Treatment of
Cancer. Lantern Slide Demonstration and Presentation of
Treated Cases.
Max Cutler.

- 9:45-10:05 Immunological Phases of Experimental Carcinoma.
Bernard Portis.
- 10:05-10:25 Studies in Cancer Immunity.
W. Saphir.
- 10:25-10:40 Lymphoblastoma: An Analysis of 130 Cases.
L. M. Rosenthal.
-

F-3

MICHAEL REESE HOSPITAL
(29th Street and Ellis Avenue)

Main Building, Fifth Floor

(Capacity—20)

- 11:00-12:00 Ward Rounds.
Sidney Strauss.
-

F-4

MICHAEL REESE HOSPITAL
(29th Street and Ellis Avenue)

Classroom of the Nurses' Home, 2816 Ellis Avenue

(Capacity—60)

- 11:00-12:00 Injuries to the Vertebrae and Intervertebral Discs Following Lumbar
Puncture.
C. N. Pease.
-

G

MUNICIPAL TUBERCULOSIS SANITARIUM
(5601 N. Crawford Avenue, at Bryn Mawr Avenue)

Amphitheatre, Fourth Floor, Middle Wing

(Capacity—60)

- 10:00-12:00 Diagnosis and Treatment of Pulmonary Tuberculosis.
Frederick Tice, Allan J. Hruby and Karl Henrichsen.

This clinic will afford opportunity for informal round table discussion of the new cases in the Receiving Ward of the institution; for the indication for treatment to be followed in the institution proper, with roentgenographic demonstrations.

H-1

NORTHWESTERN UNIVERSITY MEDICAL SCHOOL
(303 East Chicago Avenue)

Room 541

(Capacity—125)

- 9:15- 9:40 Diffuse Osteoporosis Chiefly Involving the Spine: Etiology and Treatment: Case Reports.
Walter H. Nadler.
- 9:40-10:00 Hemolytic Icterus.
William H. Holmes.
- 10:00-10:30 Early Symptoms and Findings of Heart Failure in Hypertension: Demonstration of Patients.
M. H. Barker.

- 10:30-11:00 The Importance of the Diuretic Management of Congestive Heart Failure: Demonstration of Patients.
Paul Starr.
- 11:00-12:00 Heart Clinic.
James G. Carr.
-

H-2 NORTHWESTERN UNIVERSITY MEDICAL SCHOOL
(303 East Chicago Avenue)

Room 267

(Capacity—25)

- 10:30-12:00 Clinic on Allergic Diseases: Demonstration of Patients and Diagnostic Procedures.
Samuel M. Feinberg.
-

H-3 PASSAVANT MEMORIAL HOSPITAL
(303 East Superior Street)

Room 218

(Capacity—20)

- 11:00-12:00 Roentgen Demonstration of Interesting Gastro-Enterologic Cases.
James T. Case.
-

I-1 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL
(1753 West Congress Street)

North Amphitheatre

(Capacity—75)

- 9:00-10:00 Penetrating Crater Ulcers of the Duodenum.
Ralph C. Brown.
- 10:00-10:30 Esophageal Obstructions.
James B. Eyerly.
- 10:30-11:00 Pyloric Stenosis in Infancy.
Arthur H. Parmelee.
-

I-2 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL
(1753 West Congress Street)

South Amphitheatre

(Capacity—100)

- 9:00-10:00 Emergency Management in Ketogenic Acidosis Complicating Diabetes Mellitus.
Leo K. Campbell.

- 10:00-11:00 Non-Surgical Relief of Bladder Neck Obstructions with a Review of 400 Cases.
H. L. Kretschmer.
-

I-3 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL
(1753 West Congress Street)

"F" Operating Room, Presbyterian Hospital

(Capacity—20)

- 9:30-10:30 Vaginal Hysterectomy.
N. Sproat Heaney.
-

I-4 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL
(1753 West Congress Street)

Room 401, Rush Medical College

(Capacity—20)

- 9:30-10:00 Change in Thyrotoxic Heart Following Operation.
Charles Bacon.
-

I-5 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL
(1753 West Congress Street)

Library—Presbyterian Hospital

(Capacity—20)

- 11:00-12:00 X-Ray Conference.
C. B. Rose and F. Squire.
-

J ST. LUKE'S HOSPITAL
(1437 South Michigan Avenue)

Nurses' Hall—2d Floor

(Capacity—250)

- 9:00- 9:45 Recent Advances in the Diagnosis and Treatment of Peripheral Vascular Disease.
Louis G. Hermann, Cincinnati, Ohio.
- 9:45-10:30 (a) Vascular Crises in High Blood Pressure.
(b) Hemorrhagic Nephritis.
(c) Heart Block and High Blood Pressure.
Arthur R. Elliott.
- 10:30-11:30 Effect of Splanchnic Section on Juvenile Diabetes.
Geza deTakats and George K. Fenn.
- 11:30-12:00 Roentgenograms of Tumors of the Bones.
E. L. Jenkinson.

K-1 VETERANS ADMINISTRATION FACILITY
(Hines, Illinois)

Amphitheatre
(Capacity—50)

- 9:30-10:15 Coronary Occlusion.
E. W. Hollingsworth.
10:15-11:00 Blood Dyscrasias.
E. W. Torrey.
-

K-2 VETERANS ADMINISTRATION FACILITY
(Hines, Illinois)

Wards
(Capacity—20)

- 11:00-12:00 Ward Rounds.
-

Thursday, April 19, 1934

A-1 UNIVERSITY OF CHICAGO—ALBERT MERRITT
BILLINGS HOSPITAL
(950 E. 59th Street)

Room P 117
(Capacity—256)

- 9:00- 9:45 Studies on the Nature and Inheritability of Cancer.
Maude Slye.
9:45-10:15 Bronchogenic Carcinoma.
Byron Francis.
10:15-10:45 Management of Carcinoma of the Esophagus.
Alexander Brunschwig and S. P. Perry.
10:45-11:15 Non-Specific Ulcerative Colitis.
Theodore E. Heinz.
11:15-11:45 Amebiasis and Amebic Dysentery.
Walter L. Palmer.
11:45-12:15 Motion Pictures of Gastrointestinal Motility.
A. J. Carlson.
-

A-2 UNIVERSITY OF CHICAGO—ALBERT MERRITT
BILLINGS HOSPITAL
(950 E. 59th Street)

Room M 137
(Capacity—85)

- 10:00-10:30 Two Cases of Rat-Bite Fever with Unusual Mode of Transmission.
Herbert S. Ripley.
10:30-10:45 The Pathogenesis of Diabetic Vulval Pruritus.
H. C. Hesseltine.
10:45-11:15 Chronic Neutropenia.
L. T. Coggeshall.
11:15-12:00 Clinic on Diseases of the Blood.
O. H. Perry Pepper, Philadelphia, Pa.

A-3 UNIVERSITY OF CHICAGO—ALBERT MERRITT
BILLINGS HOSPITAL
(950 E. 59th Street)

Outside of Room P 118

(No Set Capacity)

9:00–12:00 The Rôle of X-Ray in the Clinical Study of Heart Disease: Exhibi-
tion of Films.
Paul C. Hodges.

A-4 UNIVERSITY OF CHICAGO—ALBERT MERRITT
BILLINGS HOSPITAL
(950 E. 59th Street)

Room P 212

(Capacity—50)

Demonstrations

10:00–11:00 Blood Dyscrasias: Microscopic Demonstration.
E. Kandel.
11:00–11:30 The Outpatient Management of Diabetes.
Florence S. Smith (Introduced by Henry L. Schmitz).
11:30–11:45 The Fundus Oculi in Relation to General Medicine.
John T. Stough.
11:45–12:00 An Apparatus for Continuous Intravenous Injections.
Henry R. Jacobs.

B CHILDREN'S MEMORIAL HOSPITAL
(700 Fullerton Avenue)

Auditorium, Nurses' Home

(Capacity—250)

Surgical Disorders of Interest to the Internist

9:00–10:00 Urology.
Herman L. Kretschmer.
10:00–11:00 General Surgery.
Albert H. Montgomery.
11:00–12:00 Orthopedics.
Fremont A. Chandler.

C-1 COOK COUNTY GRADUATE SCHOOL OF MEDICINE
(In affiliation with the Cook County Hospital)
COOK COUNTY HOSPITAL
(West Harrison and South Wood Streets)

Medical Amphitheatre

(Capacity—150)

9:00– 9:45 Differential Diagnosis.
Frederick Tice.

- 9:45-10:30 Diabetes.
Clarence J. McMullen.
- 10:30-11:15 Some Aspects of Allergy.
Leon Unger.
- 11:15-12:00 Cardiac Pain.
Don C. Sutton.
-

C-2 COOK COUNTY GRADUATE SCHOOL OF MEDICINE
COOK COUNTY HOSPITAL
(West Harrison and South Wood Streets)

Surgical Amphitheatre

(Capacity—150)

- 9:00- 9:45 Pulmonary Diseases.
Isadore A. Rabens.
- 9:45-10:30 Diseases of the Chest.
Ellis B. Freilich.
- 10:30-11:15 Pulmonary Diseases.
Samuel J. Taub.
- 11:15-12:00 Pneumoconiosis and Tuberculosis.
S. A. Levinson.
-

C-3 COOK COUNTY GRADUATE SCHOOL OF MEDICINE
COOK COUNTY HOSPITAL
(West Harrison and South Wood Streets)

Amphitheatre, Children's Building

(Capacity—100)

- 9:00- 9:45 Diagnostic Value of Spinal Fluid.
Abraham Levinson.
- 9:45-10:30 The Problem of the Premature.
Julius H. Hess.
- 10:30-11:15 Treatment of Congenital Syphilis.
Samuel J. Hoffman.
- 11:15-12:00 Acute Otitis Media in Childhood.
Alfred Lewy.
-

C-4 COOK COUNTY GRADUATE SCHOOL OF MEDICINE
COOK COUNTY HOSPITAL
(West Harrison and South Wood Streets)

Bedside Clinics

(Capacity—15)

- C-4a 9:00-11:00 Ward 65.
Eugene F. Traut.
- C-4b 10:30-12:00 Ward 64.
Italo F. Volini.
- C-4c 11:00-12:00 Ward 61.
Frederick Tice.
- C-4d 11:00-12:00 Ward 64.
LeRoy H. Sloan.

D

UNIVERSITY OF ILLINOIS
(1817 W. Polk Street)

Room 106

(Capacity—200)

Carl A. Hedblom Presiding

- 9:00–9:20 Primary Carcinoma of the Lung, a Clinical and Pathological Report of 75 Cases.
S. A. Levinson.
- 9:20–9:40 Lung Tumors from the Radiological Viewpoint.
Adolph Hartung.
- 9:40–10:00 Indications for and Results of Therapeutic Pneumothorax.
Benjamin Goldberg.
- 10:00–10:20 Surgical Aspects and Demonstration of Cases.
Carl A. Hedblom.
- 10:20–10:40 Thromboangiitis Obliterans and Arteriosclerosis.
George Milles.
- 10:40–11:00 Methods of Evaluating the Element of Vasomotor Spasm in Thromboangiitis Obliterans.
W. J. Gillesby.
- 11:00–11:20 Cervicodorsal and Lumbar Sympathectomy in the Treatment of Thromboangiitis Obliterans and Raynaud's Disease.
Carl A. Hedblom.
- 11:20–11:40 Diagnosis and Treatment of Bronchiectasis: Case Demonstrations.
I. D. Thrasher.
- 11:40–12:00 Moving picture films showing end results.

E

LOYOLA UNIVERSITY and MERCY HOSPITAL
(2537 Prairie Avenue)

Amphitheatre

(Capacity—350)

- 9:00–10:00 Endocrine Clinic.
A. W. Schram.
- 10:00–11:00 Gastrointestinal Clinic.
Fred M. Drennan.
- 11:00–12:00 Cardiorenal Clinic.
Milton Mandel.

F-1

MICHAEL REESE HOSPITAL
(29th Street and Ellis Avenue)

Sarah Morris Amphitheatre, 2901 Ellis Avenue

(Capacity—170)

*Heart Study Group**Recent Studies of Cardiovascular Disease*

- 9:00–9:15 Chorea.
Jesse R. Gerstley.

- 9:15- 9:30 Convalescent Care of Cardiac Children.
Philip Rosenblum.
- 9:30- 9:40 The Relation of Subacute Bacterial Endocarditis to Rheumatic Endocarditis.
S. Wile and Otto Saphir.
- 9:40- 9:50 Treatment of Subacute Bacterial Endocarditis.
Walter W. Hamburger.
- 10:00-10:20 Peripheral Vascular Disorders.
S. Perlow.
- 10:25-10:35 A Method of Obtaining Heart Size Roentgenographically in Bedridden Patients at Ordinary Target Distance.
J. Brams, W. Brams and R. Arens.
- 10:40-10:55 Recent Observations on the Genesis of the Electrocardiogram.
L. N. Katz.
-

F-2

MICHAEL REESE HOSPITAL
(29th Street and Ellis Avenue)

Rothschild Amphitheatre, 2816 Ellis Avenue
(Capacity—330)

Peptic Ulcer

- 9:00- 9:20 Pathology.
Otto Saphir.
- 9:20- 9:40 Physiology.
H. Necheles.
- 9:40-10:00 Medical.
Jacob Meyer.
- 10:00-10:20 Surgical.
A. A. Strauss.
- 10:20-10:40 Roentgenology.
Robert Arens.
- 10:40-11:00 Discussion: To be opened by
Walter Alvarez, Mayo Clinic, Rochester, Minn.
-

F-3

MICHAEL REESE HOSPITAL
(29th Street and Ellis Avenue)

Ward of Main Building, Fifth Floor
(Capacity—20)

- 11:00-12:00 Correlation of the Eye Findings in General Medical Conditions.
L. L. Mayer.
-

F-4

MICHAEL REESE HOSPITAL
(29th Street and Ellis Avenue)

Classroom of the Nurses' Home, 2816 Ellis Avenue
(Capacity—60)

- 11:00-12:00 Perirenal Infections.
H. C. Rolnick.

G

MUNICIPAL TUBERCULOSIS SANITARIUM
(5601 N. Crawford Avenue, at Bryn Mawr Avenue)

Surgical Amphitheatre, Fourth Floor, Middle Wing

(Capacity—50)

9:00–12:00 Surgical Clinic.

Richard Davison.

This clinic will afford opportunity to observe the treatment of tuberculosis by surgical methods, such as thoracoplasty, phrenico-exeresis, intra- and extrapleural pneumolysis.

H-1 NORTHWESTERN UNIVERSITY MEDICAL SCHOOL
(303 East Chicago Avenue)

Institute of Neurology—Room 541

(Capacity—125)

9:15– 9:45 Diagnostic Significance of Pupillary Changes: Demonstration of Cases.
Lewis J. Pollock.

9:45–10:00 The Pathway for the Pupillary Light Reflex.
S. W. Ranson.

10:00–10:20 Some Aspects of Epilepsy.
Harry A. Paskind.

10:20–10:40 Blood Bromide Control of Epilepsy.
Benjamin Boshes.

10:40–11:00 The Influence of Hyperthyroidism on the Phospholipids of the Brain.
Arthur Weil.

11:00–12:00 Clinical and Experimental Relation of Pituitary, Hypothalamus and
Sugar Metabolism.
David Cleveland and Loyal Davis.

H-2 NORTHWESTERN UNIVERSITY MEDICAL SCHOOL
(303 East Chicago Avenue)

Room 393

(Capacity—20)

10:00–11:00 Physical Therapy in Arthritis: Demonstration of a Program for Home
and Office Treatment.
John S. Coulter.

11:00–12:00 Demonstration of Capillary Changes Following Physiotherapeutic
Measures.
Gilbert H. Marquardt.

H-3

PASSAVANT MEMORIAL HOSPITAL
(303 East Superior Street)

No Program on Thursday

I-1 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL
(1753 West Congress Street)

North Amphitheatre

(Capacity—75)

- 9:00- 9:30 Present Status of Coronary Thrombosis.
James B. Herrick.
- 9:30-10:00 Certain Features of Treatment of Cardiac Failure.
Fred M. Smith, Iowa City, Iowa.
- 10:00-10:15 Value of Serial Electrocardiograms in Coronary Thrombosis.
H. A. Richter.
- 10:15-11:00 A Moving Picture Showing the Relation of the Cardiac Cycle to the
Electrocardiogram.
Clayton J. Lundy.
-

I-2 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL
(1753 West Congress Street)

South Amphitheatre

(Capacity—100)

- 9:00-10:30 Thyroid Clinic.
W. O. Thompson.
James H. Means, Boston, Mass.
- 10:30-11:00 Cryptogenic Fever in Ichthyosis.
Rollin T. Woodyatt.
-

I-3 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL
(1753 West Congress Street)

Room 302

(Capacity—20)

- 10:00-10:30 Cardiac Disease in Pediatric Practice.
Charles K. Stulik.
- 10:30-11:00 Migraine.
Peter Bassoe.
-

I-4 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL
(1753 West Congress Street)

Library, Presbyterian Hospital

(Capacity—20)

- 11:00-12:00 Pathology Conference Demonstrating Some Recent Concepts of Ne-
phritis and Cirrhosis.
Carl W. Apfelbach.

J

ST. LUKE'S HOSPITAL
(1437 South Michigan Avenue)

Nurses' Hall—2d Floor

(Capacity—250)

- 9:00– 9:45 Congenital Heart Disease.
Louis F. Bishop, Jr., New York, N. Y.
- 9:45–10:30 Presentation of Brain Tumors with Roentgenograms.
Eric Oldberg.
- 10:30–11:15 The Importance of Cranial Roentgenograms in Neurosurgical Problems.
W. McKendree Craig, Rochester, Minn.
- 11:15–12:00 The Anemias.
John H. Musser, New Orleans, La.

Friday, April 20, 1934

A-1 UNIVERSITY OF CHICAGO—ALBERT MERRITT
BILLINGS HOSPITAL
(950 E. 59th Street)

Room P 117

(Capacity—256)

- 9:00– 9:30 Hormones and Mammary Glands.
Carl R. Moore.
- 9:30–10:00 Recent Studies on the Male Hormone.
Fred C. Koch.
- 10:00–10:30 Indications of Hormonal Influences, other than Insulin, on Carbohydrate Metabolism.
B. O. Barnes.
- 10:30–11:00 Demonstration of Clinical Endocrinopathies.
Allen T. Kenyon.
- 11:00–12:00 Clinic on Thyroid Disease.
James H. Means, Boston, Mass.

A-2 UNIVERSITY OF CHICAGO—ALBERT MERRITT
BILLINGS HOSPITAL
(950 E. 59th Street)

Room M 137

(Capacity—85)

- 9:00– 9:30 The Etiology of Gallstones.
Edmund Andrews.
- 9:30–10:15 Calcium Salts in Gallstones.
Dallas B. Phemister.
- 10:15–10:45 The Etiology of Non-Obstructive Jaundice.
E. S. Guzman Barron.
- 10:45–11:15 Toxic Hepatitis Due to Cinchophen.
Henry T. Ricketts.
- 11:15–12:00 Glycogen Storage Disease.
E. M. Humphreys.

Outside of Room P 118

(No Set Capacity)

9:00-12:00 The Rôle of X-Ray in the Clinical Study of Heart Disease: Exhibition of Films.
Paul C. Hodges.

Auditorium, Nurses' Home

(Capacity—250)

10:00–11:00 Behavior Problems in Children.

Bert I. Beverly.

11:00-12:00 Speech Defects in Children.
Frances Perlowski.

Medical Amphitheatre

(Capacity—150)

9:00- 9:45 Differential Diagnosis of Abdominal Pain.
Lee C. Gatewood.

9:45-10:30 Auricular Fibrillation.
Chauncey C. Maher.

10:30-11:15 Amebic Dysentery.
Alexander A. Goldsmith.

11:15-12:00 Pathology of Primary Carcinoma of Lung.
R. H. Jaffé.

Surgical Amphitheatre

(Capacity—150)

9:00- 9:45 Pulmonary Tuberculosis.
N. I. Fox.

9:45-10:30 X-Ray Studies in Pulmonary Tuberculosis.
Harry H. Freilich.

10:30-11:15 Diagnosis of Pulmonary Tuberculosis.
Harry S. Arkin.

C-3 COOK COUNTY GRADUATE SCHOOL OF MEDICINE
COOK COUNTY HOSPITAL
(West Harrison and South Wood Streets)
Amphitheatre, Children's Building
(Capacity—100)

9:00- 9:45 Diagnosis of Syphilis in the Newly Born.
Arthur H. Parmelee.
9:45-10:30 Physical Examination of Younger Children.
Henry E. Irish.
10:30-11:15 Convalescent Serum in the Treatment of Contagious Disease.
Archibald Hoyne.
11:15-12:00 Urinary Retention in Childhood.
Patrick H. McNulty.

C-4 COOK COUNTY GRADUATE SCHOOL OF MEDICINE
COOK COUNTY HOSPITAL
(West Harrison and South Wood Streets)
Bedside Clinics
(Capacity—15)

C-4a 9:00-11:00 Ward 61.
Lee C. Gatewood.
C-4b 10:00-12:00 Ward 45.
Samuel M. Feinberg.
C-4c 10:00-12:00 Ward 63.
Sidney A. Portis.
C-4d 10:00-12:00 Ward 60.
Leon Unger.

D UNIVERSITY OF ILLINOIS
(1817 W. Polk Street)
Room 106
(Capacity—200)

Hugh A. McGuigan and William F. Petersen Presiding
9:00- 9:20 The Effect of Air Filtration on Seasonal Hay Fever and Pollen
Asthma.
Tell Nelson and W. H. Welker.
9:20- 9:40 The Effect of Viosterol of High Potency on Seasonal Hay Fever and
Asthma.
Ben Z. Rappaport.
9:40-10:00 Calcium Metabolism in Relation to High Viosterol Dosages.
C. I. Reed.
10:00-10:20 Effect of Ultraviolet Light on Sympatheticomimetic Drugs.
Hugh A. McGuigan and P. L. Ewing.
10:20-10:40 Hyperparathyroidism.
Lindon Seed.

- 10:40-11:00 A Cephalometric, Radiographic, Histologic Analysis of Dental Conditions in a Hypopituitary Case.
I. Schour and A. J. Brodie.
- 11:00-11:20 Creatine Metabolism in Childhood.
H. G. Poncher.
- 11:20-11:40 The Association of Meteorological Conditions and Diseases in General.
William F. Petersen.

E LOYOLA UNIVERSITY and MERCY HOSPITAL
(2537 Prairie Avenue)

Amphitheatre
(Capacity—350)

- 9:00-10:00 General Medicine.
Walter G. McGuire.
- 10:00-11:00 Clinico-Pathological Conference.
E. L. Benjamin.
- 11:00-12:00 Cardiac Clinic.
Robert S. Berghoff.

F-1 MICHAEL REESE HOSPITAL
(29th Street and Ellis Avenue)

Sarah Morris Amphitheatre, 2901 Ellis Avenue
(Capacity—170)

Diseases of the Chest and Infectious Diseases

- 9:00- 9:20 Indications for Compression Therapy in Pulmonary Tuberculosis.
M. Biesenthal.
- 9:20- 9:40 Results Following Compression Therapy in Pulmonary Tuberculosis,
X-Ray Case Demonstration and Follow-Up Statistics: Resumé of
Work of Last Eight Years.
R. Bettman.
- 9:40-10:00 Studies on the Effects of Breathing Oxygen and Carbon Dioxide En-
riched Atmospheres.
D. J. Cohn.
- 10:00-10:20 Results of Convalescent Serum Therapy during Past Three Years.
S. O. Levinson.
- 10:20-10:40 The Treatment of Empyema Thoracis; Explanation of the Rationale
of the Closed Method of Drainage: Moving Picture Demonstra-
tion.
R. Bettman.

F-2 MICHAEL REESE HOSPITAL
(29th Street and Ellis Avenue)

Rothschild Amphitheatre, 2816 Ellis Avenue
(Capacity—330)

Metabolism Group. Diabetes Mellitus

- 9:00- 9:25 Newer Trends in the Treatment of Diabetes Mellitus.
Solomon Strouse.

- 9:30- 9:50 The Eye in Diabetes Mellitus.
H. Gradle.
- 9:55-10:20 The Metabolic Disturbance in Diabetes.
S. Soskin.
- 10:25-10:40 The "Diabetogenic" Hormone.
L. B. Shpiner.
- 10:45-11:00 Feeding the Diabetic Patient in an Outpatient Clinic.
Sarah Elkin.

F-3

MICHAEL REESE HOSPITAL
(29th Street and Ellis Avenue)

Sarah Morris Hospital, 1st Floor, 2901 Ellis Avenue
(Capacity—60)

Stomach Group

- 9:00- 9:10 A Preliminary Report on the Secretion and Motility of the Stomach after Subtotal Gastrectomy.
Sigfried Strauss, A. A. Strauss, L. Scheman and H. Necheles.
- 9:10- 9:20 The Treatment of Peptic Ulcer with Powdered Okra.
Jacob Meyer and H. Necheles.
- 9:20- 9:30 Peptic Ulcer and Diabetes—Renal Glycosuria.
H. Binswanger and Jacob Meyer.
- 9:30- 9:50 Ulcerative Colitis; a Symposium: Medical and Surgical Aspects.
A. A. Strauss and Jacob Meyer.
- 9:50- 9:55 Duodenal Carcinoma; Report of Four Cases: Demonstrations of Specimens.
D. Rosenberg and Jacob Meyer.
- 9:55-10:10 The Effects of Peppermint Oil on Gastric Secretion and Motility.
Jacob Meyer, L. Scheman and H. Necheles.
- 10:10-10:25 The Effect of Peppermint Oil on Gastric Motility.
H. Sapoznik, R. Arens, H. Necheles and Jacob Meyer.
- 10:25-10:30 Teaching the Gastrointestinal Patient How to Eat.
Sarah Elkin and Jacob Meyer.
- 10:30-10:35 The Management of the Stomach Clinic.
Jacob Meyer and A. A. Strauss.
- 10:35-10:50 Chronic Jaundice.
A. A. Strauss.

G-1

MUNICIPAL TUBERCULOSIS SANITARIUM
(5601 N. Crawford Avenue, at Bryn Mawr Avenue)

Amphitheatre, Fourth Floor, Middle Wing
(Capacity—60)

- 10:00-12:00 Clinical Conference on the Surgical Treatment of Tuberculosis.
Richard Davison, Karl Henrichsen and Frank Fremmel.

This clinic will afford an informal round table discussion of cases that have been treated with the various forms of collapse therapy, with demonstration of the cases and roentgenograms.

G-2 MUNICIPAL TUBERCULOSIS SANITARIUM
 (2049 Washington Boulevard)
 (Capacity—6)

10:00-12:00 An Extramural Pneumothorax Clinic.
 Minas Joannides, Edmund L. Quinn, Emil Bunta and Clara Jacobson.

This clinic will afford opportunity to observe the actual technical work in pneumothorax therapy.

H-1 NORTHWESTERN UNIVERSITY MEDICAL SCHOOL
 (303 East Chicago Avenue)
 Room 541
 (Capacity—125)

9:15- 9:40 The Use of Chondroitin in the Treatment of Migraine, with Demonstration of Patients.
 L. A. Crandall.

9:40- 9:55 Blood Changes Following Gastrectomy in the Rat.
 Frederick Jung.

9:55-10:20 Experimental Studies on the Etiology of Anemia in Man and in Animals.
 A. C. Ivy.

10:20-10:50 Treatment of Deficiency Anemias: Presentation of Patients.
 Howard Alt.

10:50-11:20 A Report on the Percentage of Recurrences of Peptic Ulcer under Mucin Management, with Demonstration of Patients.
 Samuel J. Fogelson.

11:20-12:00 Experimental Studies on the Value of Mucin in Peptic Ulcer.
 A. C. Ivy, G. B. Fauley, John Orndoff and P. E. Reid.

H-2 NORTHWESTERN UNIVERSITY MEDICAL SCHOOL
 (303 East Chicago Avenue)
 Room 267
 (Capacity—25)

10:30-12:00 Clinic on Allergic Diseases: Demonstration of Patients and Diagnostic Procedures.
 Samuel M. Feinberg.

H-3 PASSAVANT MEMORIAL HOSPITAL
 (303 East Superior Street)
 Room 108
 (Capacity—20)

10:30-12:00 Oxygen Therapy: Demonstration of Oxygen Chamber, Tent and Catheter Technic.
 M. H. Barker.

1194

PROGRAM OF THE CHICAGO MEETING

H-4

PASSAVANT MEMORIAL HOSPITAL
(303 East Superior Street)

Room 218

(Capacity—25)

11:00–12:00 Roentgen Demonstration of Interesting Gastro-Enterologic Cases.
James T. Case.

I-1 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL

(1753 West Congress Street)

North Amphitheatre

(Capacity—75)

9:00– 9:45 Recent Concepts of Arthritis.

Ernest E. Irons.

9:45–10:30 Chronic Arthritis with Special Reference to Treatment.

Russell L. Cecil, New York, N. Y.

10:30–11:15 Liver Function Tests.

William J. Kerr, San Francisco, Calif.

11:15–12:00 Familial Icterus.

Evans W. Pernokis.

I-2 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL

(1753 West Congress Street)

South Amphitheatre

(Capacity—100)

9:00–10:00 Chronic Subdural Hematomas.

A. Verbrugghen.

10:00–11:00 Cardiac Arrhythmias.

Frank B. Kelly.

11:00–12:00 Renal Damage in Prostatic Obstruction Due to Bladder Compensation.

Robert H. Herbst.

I-3 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL

(1753 West Congress Street)

Room 302

(Capacity—20)

10:00–11:15 Modern Treatment of Pseudohypertrophic Muscular Dystrophy.

Richard B. Richter.

11:15–12:00 Lead Poisoning.

William D. McNally.

I-4 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL
(1753 West Congress Street)

Room 401
(Capacity—20)

- 10:00-11:00 Surgery of the Thyroid Gland.
Edwin M. Miller.
11:00-11:30 Liver Treatment in Agranulocytosis.
R. W. Trimmer, H. M. Sheaff and F. L. Foran.
11:30-12:00 Neurological Clinic.
James C. Gill.
-

I-5 RUSH MEDICAL COLLEGE and THE PRESBYTERIAN
HOSPITAL
(1753 West Congress Street)

Library, Presbyterian Hospital
(No Capacity Indicated)

- 11:15-12:00 The Use of High Protein in Reducing Diets.
Anna E. Boller.
-

J ST. LUKE'S HOSPITAL
(1437 South Michigan Avenue)

Nurses' Hall—2d Floor
(Capacity—250)

- 9:00-10:30 General Medical Clinic—"Weekly Grand Rounds."
Staff of St. Luke's Hospital.
10:30-11:00 Treatment of Angina Pectoris.
N. C. Gilbert.
11:00-12:00 Pathological Demonstrations.
Edwin F. Hirsch.

COLLEGE NEWS NOTES

GIFTS ACKNOWLEDGED

The following members have donated publications of which they are the authors, as indicated below, to the Library of the College. It is intended that this Library be a memorial to our members and consist principally of books of which members of the College are authors or joint authors.

Dr. J. Arnold Bargen (Fellow), Rochester, Minn.—1 book, "The Colon, Rectum and Anus";

Dr. I. M. Rabinowitch (Fellow), Montreal, Que.—1 book, "Diabetes Mellitus, A Handbook of Simplified Methods of Diagnosis and Treatment";

Dr. Joseph Hajek (Associate), New York, N. Y.—1 reprint;

Dr. James H. Hutton (Associate), Chicago, Ill.—6 reprints;

Dr. David E. Markson (Fellow), Chicago, Ill.—1 reprint;

Dr. Philip B. Matz (Fellow), Washington, D. C.—1 report on the residual effects of warfare gases;

Dr. Lewis J. Moorman (Fellow), Oklahoma City, Okla.—14 reprints.

NEW LIFE MEMBERS

Dr. Samuel E. Thompson (Fellow), Kerrville, Texas, and Dr. Philip H. Jones (Fellow), New Orleans, La., have become Life Members of the American College of Physicians, having contributed the prescribed life membership fee in accordance with the new plan of life membership recently adopted.

Dr. John Dudley Dunham (Fellow), for many years Governor of the College for the State of Ohio, was recently chosen chief of the general staff of the Grant Hospital, Columbus. Dr. Dunham is also medical consultant for the Franklin County Tuberculosis Sanitarium and a member of the staffs of the Mt. Carmel and White Cross Hospitals.

Dr. George R. Minot (Fellow), Boston, Mass., Professor of Medicine, Harvard University, delivered the twelfth lecture of the eighth series of afternoon lectures sponsored by The New York Academy of Medicine, on January 26. Dr. Minot's subject was "The Anemias—Etiology and Treatment."

Dr. Donald Gregg (Fellow), Wellesley, Mass., is President of the Massachusetts Society for Mental Hygiene.

Dr. J. Stuart McQuiston (Associate), formerly located in Rochester, Minn., removed on February 1, 1934, to 317 Higley Bldg., Cedar Rapids, Iowa, where he is engaged in private practice.

Dr. Mark S. Knapp (Fellow), Flint, Mich., has retired from private practice and is devoting his entire time as Director of Medical Research of the Horace H. and Mary A. Rackham Fund.

Dr. Samuel Weiss (Fellow), New York, N. Y., has been appointed Editor of *The Review of Gastroenterology*, the official organ of the Society for the Advance-

ment of Gastroenterology. This journal made its initial appearance February 15, as a quarterly journal devoted to gastroenterology, proctology and allied subjects.

The Wyatt Research Foundation has been incorporated in the State of Arizona, "to conduct scientific investigations relative to the treatment and prevention of disease (particularly the arthritides) and the advancement of clinical and scientific medicine." The incorporators named are: Dr. Bernard L. Wyatt (Fellow), Laura W. Wyatt and Thelma G. Ream.

Dr. S. A. Slater (Fellow), Worthington, Minn., presided as President over the Thirty-Ninth Annual Session of the Sioux Valley Medical Association at Sioux City, Iowa, January 23-24.

At the last annual business meeting of the Institute of Medicine of Chicago, Dr. Joseph L. Miller (Fellow) was elected President and Dr. John Favill (Fellow), Treasurer.

Dr. John E. Gordon (Fellow), Detroit, Mich., will be in charge of the new department of Epidemiology of the W. K. Kellogg Foundation. The department was established for the purpose of research in the control of communicable disease.

Dr. Lewellys F. Barker (Fellow), Baltimore, Md., was elected a Vice-President of the Association for Research in Nervous and Mental Disease, at its last annual meeting in New York City.

Dr. Bailey K. Ashford (Fellow), San Juan, Puerto Rico, recently retired as a colonel of the Medical Corps, U. S. Army, has been honored by the unanimous vote of the legislature of Puerto Rico in recognition of his being the founder of the School of Tropical Medicine and the initiator of the first campaign against hookworm disease in America. A bronze bust of Dr. Ashford will be placed in the government building in San Juan.

Dr. Edward B. Vedder (Fellow), Washington, D. C., is President-Elect of the American Society of Tropical Medicine.

Dr. Mills Sturtevant (Fellow) was recently appointed Professor of Clinical Medicine at New York University, and Dr. Warren Coleman (Fellow) was made Professor Emeritus of Clinical Medicine.

Dr. Hugh Rodman Leavell (Fellow) has been appointed Health Commissioner of Louisville, Ky.

Dr. Raphael Isaacs (Fellow), Ann Arbor, Mich., Dr. John A. E. Eyster (Fellow), Madison, Wis., and Dr. Andrew C. Ivy (Fellow), Chicago, Ill., delivered lectures in connection with a series of graduate lectures in physiology at Marquette University Medical School, sponsored by the educational committee of the Medical Society of Milwaukee County, during February and March.

Dr. George E. Pfahler (Fellow), Philadelphia, Pa., appears on the program of the fourth International Congress of Radiology, to be held in Zurich, July 24-31.

The College of Physicians of Philadelphia and the American Academy of Political and Social Science held a joint meeting, February 7, for the discussion of "The Medical Profession and the Public: Currents and Countercurrents." Dr. Nathan B. Van Etten (Fellow), New York, spoke on "Abuses of Medical Charity and of the Free Services of Physicians." Dr. Roger I. Lee (Fellow), Boston, spoke on "The General Practitioner: His Place in the Medical Profession."

OBITUARIES

DR. JULIAN TURNBULL McCLYMONDS

Dr. Julian Turnbull McClymonds died December 4, 1933, in Berkeley, California. Dr. McClymonds was born in Winchester, Kentucky, November 26, 1870. He received his pre-medical training at the University of Kentucky and his M.D. from the University of Michigan Medical School, 1894; he did postgraduate work at the University of Vienna, University of Paris and Mt. Vernon Hospital. The greater part of his professional life was spent in Lexington, Kentucky, where he was a member of the Lexington Clinic from 1920 to 1931. He was First Assistant Surgeon, University of Michigan Medical School, 1894-1895; First Assistant in Hygiene and Physiological Chemistry at the same school, 1896-1898; Consulting Physician Good Samaritan and St. Joseph's Hospitals, Lexington, Kentucky, 1912-1931; assisted in organizing Hospital Unit No. 40, "The Barrow Unit," for service in the World War, and during his service in this country and in France, he was promoted from the rank of Lieutenant to that of Lieutenant Colonel, being retired from active service at the close of the war and commissioned a Colonel of Reserves, U. S. Army Medical Corps. He was a member of his County and State societies, a Fellow of the American Medical Association, Southern Medical Association and a Fellow of the American College of Physicians since 1920. He retired from practice in Lexington and went to Berkeley, California, where his death occurred as a result of heart disease.

ERNEST B. BRADLEY, M.D., F.A.C.P.,
Governor for Kentucky.

DR. GEORGE HUNTER

Dr. George Hunter (Fellow), died on December 12, 1933. Dr. Hunter was born in Illinois. He early came to California. He was graduated from the College of the University of California, at Berkeley, in 1903. In 1906 he received the degree of Doctor of Medicine from the same institution. In 1907 he came to Los Angeles and began the practice of medicine.

Dr. Hunter was an outstanding member of both the Los Angeles County Medical Association and the California State Association, having held offices and sat in the Councils of both of these organizations. He held many positions of honor and trust in the medical societies to which he belonged. He was a Past President of the Los Angeles County Medical Association, of the Clinical and Pathological Society, and of the Society for Psychiatry and Neurology. He was a member of the Board of Councilors of the California Medical Association, a Fellow of the American College of Physicians, a member of the Psychopathic Association of California, and a member of the Insanity Commission of the State. He was a member of the Staff of the Los Angeles General Hospital for twenty years and served on the Staffs of St. Vincent's, the Cedars of Lebanon, California and the Santa Fe Hospitals. During the War, Dr. Hunter was a Captain in the Medical Corps with Base Hospital Number 35 in France. In addition to these activities and the crowded days of a busy life he found time for special study periods in the neurologic centers of Philadelphia, Boston and Baltimore.

The Associations to which Dr. Hunter belonged and scientific medicine, especially in the fields of neurology and psychiatry, have sustained a great loss in his death. The community in which he lived will miss an earnest medical practitioner and civic worker. Dr. Hunter had a most pleasing personality. His attachments were full and deep. He was a friendly man and his friendship was given without reservations. His death came as a shock to the members of the profession and the citizens of the community in which he lived. The memory of the man and of the good he did will long be with us.

EGERTON CRISPIN, M.D., F.A.C.P.,
Governor for Southern California.

DR. ARTHUR D. DUNN

Dr. Arthur D. Dunn (Fellow), Omaha, Nebraska, died January 8, 1934, from a heart affection; aged sixty-six years.

Dr. Dunn was a native of Meadville, Pa. He held the degree of Bachelor of Arts from Allegheny College, 1896; Doctor of Philosophy from the University of Chicago, and Doctor of Medicine from Rush Medical College, 1892. He was house physician at Cook County Hospital and a private assistant to Dr. John B. Murphy. He went to Omaha in 1907, and is said to have been the earliest exponent of real scientific medicine in the Missouri Valley. He was coroner's physician in Omaha for one and one-half years, exerting great influence in the introduction of the value of autopsies to members of the profession of Omaha. Dr. Dunn was professor of medicine at Creighton University College of Medicine from 1908 to 1922; a member of the Advisory Board and vice-dean of the same institution from 1914 to 1922; professor of experimental medicine and chairman

of the Department of Clinical Research at Nebraska University College of Medicine from 1924 to the time of his death.

He was a member of the Nebraska State Medical Association and served as its delegate to the American Medical Association several years. He was a Fellow of the American Medical Association and served on its Council on Medical Education a number of years. He was also a member of the Central Society for Clinical Research, past president of the Missouri Valley Medical Society, and president-elect of the Omaha-Mid-West Clinical Society. He was elected a Fellow of the American College of Physicians in 1918, and served for several years as the Governor of the College for Nebraska.

Dr. Dunn was the author of numerous scientific articles appearing in leading medical journals, and was much in demand as a speaker at medical meetings, locally and nationally.

ADOLPH SACHS, M.D., F.A.C.P.,
Governor for Nebraska.

NATIONAL PNEUMONIA SERA



The Research Laboratories of The National Drug Company have made close studies of producing and refining Pneumonia Serum. Methods of immunizing horses, and processes of concentrating and refining the serum, have been devised enabling us to offer a refined and concentrated product approximating six to ten times the potency of the unrefined serum, with a corresponding decrease of inert solids and proteins. Refined Pneumonia Serum approximates 10,000 Felton Units per 10 cc. and in addition contains all other antitoxic or protective substances contained in the whole serum.

The chill producing substances have largely been removed.

Doses of 10 to 20 cc., repeated every six to eight hours, or as advisable, may be given until a favorable response is secured. The patient's sputum should be typed early and if Type I, II or III pneumococci are present the serum should be continued. When the type of pneumococcus in the sputum and blood is represented by antibodies or protective substances in the serum, reports from physicians show a fall in the patient's temperature as soon as sufficient serum has been given to overcome the bacteriemia and toxemia. Early and adequate doses of serum are essential to overcome the infection.

Refined Pneumonia Serum is furnished in 10 cc. perfected syringes, with chromium (rustless steel) intravenous needles, and in 20 cc. syringes and ampoule-vials.

For Quick Pneumonia Type Diagnosis

We prepare monovalent pneumonia typing serums for rapid typing of pneumonia by the Neufeld (quellung) reaction described by A. B. Sabin (Jour. Am. Med. Asso. 5-20-33 fol. 1584).

PTD-I	Five Tests (5 capillary tubes)	Type I	\$0.50
PTD-II	Five " (5 " ")	Type II	.50
PTD-III	Five " (5 " ")	Type III	.50

Detailed information on request.

THE NATIONAL DRUG COMPANY
PHILADELPHIA
U.S.A.



Send detailed information on Refined Pneumonia Serum per Annals of Internal Medicine.

Name State

City Date

EIGHT YEARS' INTENSIVE SCIENTIFIC RESEARCH HAS PRODUCED WHITE'S COD LIVER OIL CONCENTRATE TABLETS

White's Cod Liver Oil Concentrate Tablets are one of the oldest stable, proven, potent, emulsifying concentrates of cod liver oil on the market. Their efficacy and scientific soundness are attested by clinical tests in recognized institutions. They stand accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

● The makers of White's Cod Liver Oil Concentrate Tablets have pioneered in the vitamin-concentrate field. Because of the time-tested therapeutic importance of cod liver oil our scientists have devoted years of effort to make the oil more palatable, easier to take—but yet to retain all the vitamin potency of the oil itself.

We designed a plant especially for the making of White's Cod Liver Oil Concentrate Tablets. We established laboratories which are among the most up to date in the country. We appointed scientists, recognized authorities in their respective fields, to work on perfecting White's Cod Liver Oil Concentrate Tablets.

And eight years of intensive scientific research have produced what we consider the perfect cod liver oil concentrate. The potency of the actual concentrate used in the making of White's Cod Liver Oil Concentrate Tablets is approximately 150 times that of liquid cod liver oil—each tablet contains not less than 1000 vitamin

A units (U.S.P.) and not less than 500 units of vitamin D (A.D.M.A.).

We put this highly potent concentrate in tablet form because the tablet is more palatable, infinitely more convenient. Its accuracy in dosage is beyond guesswork . . . no liquid to spill . . . no deterioration of vitamin potency.

Naturally, the real test of any medical product is how it works clinically. White's Cod Liver Oil Concentrate Tablets have been tested clinically in leading institutions. These tests have convincingly proved the merit of White's Cod Liver Oil Concentrate Tablets.

Food Value Chart and Professional Sample to Physicians

On request, we shall send you a professional sample of White's Cod Liver Oil Concentrate Tablets. Also an interesting food chart which gives you the value of foods—vitamins, proteins, fats, carbohydrates, minerals—acid and alkaline reactions—all at a glance—just by revolving a wheel. Very convenient. Address Health Products Corporation, 113 N. 13th Street, Newark, N. J., Department F-5. Please use your prescription form or letterhead.

White's COD LIVER OIL
CONCENTRATE TABLETS



AMERICAN JOURNAL OF
DIGESTIVE DISEASES
AND NUTRITION

ican College of Physicians for the very satisfactory reception accorded by them to this new publication. ¶It is the aim of this Journal to maintain itself on a high scientific and clinical plane. To achieve such position the Journal is open at all times to constructive suggestions and criticisms. The submission of original contributions is encouraged. They will receive prompt consideration by members of the Editorial Council and the Editor-In-Chief. Manuscripts should be forwarded to Dr. Frank Smithies, 920 North Michigan Avenue, Chicago, Illinois.

✂ ✂ ✂ ✂ ✂ ✂ ✂ ✂ ✂ ✂

THE Editors and the Council of the American Journal of Digestive Diseases and Nutrition wish to take this opportunity of thanking Fellows and Associates of the Amer-

American Journal of Digestive Diseases and Nutrition
435-455 Lincoln Bank Tower,
Fort Wayne, Indiana.

Gentlemen:

I wish to subscribe to your Journal

- ☐ (a) For 1 year\$ 6.00
☐ (b) For 2 years\$11.00
☐ (c) For 3 years\$16.00

Inclosed please find my check.

Name.....

Address.....

A Pure, Palatable, Carbonated

PREPARED WATER



Kalak Water is made of carbonated distilled water and chemically pure salts of calcium bicarbonate, sodium chloride, sodium phosphate and bicarbonates of magnesium, potassium and sodium.

THERE are many conditions, no doubt, where you will want your patient to increase his daily intake of water.

In such cases, why not suggest the use of Kalak Water, the palatable, carbonated alkaline water prescribed by physicians for over twenty years.

Kalak

TRADE MARK U.S. PAT. OFF.

Please Mention this Journal when writing to Advertisers

CURDOLAC FOODS LENGTHEN DIABETIC LIVES

Blood sugar producing properties are low because these foods are:

1. Moderate in carbohydrate content, yet
2. Not excessive in protein and fat.

(58% of the proteins and 10% of the fat consumed produce sugar in the blood.)

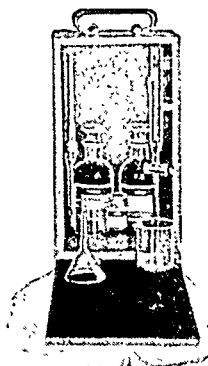
Samples and literature on request.

CURDOLAC FOOD CO.

Box 299

Waukesha, Wis.

LAMOTTE Blood Chemistry SERVICE



Blood Urea Outfit

For study of urea retention (urea nitrogen by factor).

Result is read directly from special Urea Burette supplied.

No calculations required.

Accurate to 4 mg. urea per 100 cc. blood.

Complete estimation takes only 15 to 20 minutes.

Price, complete with instructions, \$18.50, f.o.b. Baltimore, Md.

LaMotte Blood Chemistry Service includes a series of similar outfits for conducting the following accurate tests.

Blood Sugar—Icterus Index—Phenolsulphophthalein—Urine pH—Blood pH—Gastric Acidity—Calcium Phosphorus—Blood Bromides—Urinalysis.

If you do not have a LaMotte Blood Chemistry Handbook, write today for a complimentary copy

LaMotte Chemical Products Co.

418 Light Street - - - Baltimore, Md.

PROFESSIONAL PROTECTION



"Some may wish you Peace and Ease
A smoother path in the year ahead.
We wish you Fiber the Valiant need
To force your way thru bitter blasts;
We wish you the heart of the Fighting Breed
To carry you on while the battle lasts."

"THE FIGHTING COMPANY"

THE MEDICAL PROTECTIVE COMPANY

OF FORT WAYNE, INDIANA

WHEATON, ILLINOIS

WANTED Copies of ANNALS OF INTERNAL MEDICINE

\$1.50 each for
Volume II, No. 5, November, 1928

\$.80 each for
Volume VI
No. 9, No. 10, and No. 11
March, April, and May, 1933

Address your journals to:

E. R. LOVELAND

Executive Secretary,

133-135 S. Thirty-sixth Street
PHILADELPHIA, PA.



In Convalescence When Feeding Is Difficult

When appetite lags, digestion is impaired and the patient balks at the very foods most needed to rebuild strength and vitality, the question of feeding the patient adequately often becomes a problem.

Here is where Ovaltine can be used to excellent advantage. Clinical experience of its use over many years shows that it can often be taken and well tolerated when other foods are rejected by the patient. It has an enticing flavor and appetite appeal, and imposes no strain upon the digestive function.

Ovaltine, too, enhances the nutritive value of the diet. It adds to it vital food elements, including the essential minerals, iron, calcium and phosphorus, as well as reinforcing the diet with important vitamins such as the appetite-producing and antineuritic vitamin B.



Ovaltine, too, considerably increases the digestibility of milk by breaking up the heavy curd of cow's milk into a light, easily digested coagulum.

Where nervous irritability, pain or worry interfere with sound sleep, a drink of warm Ovaltine often works wonders and lulls the patient into refreshing slumber without the use of drugs.

✦ ✦ ✦

Why not let us send you a trial supply of Ovaltine? If you are a physician, dentist or nurse, you are entitled to a regular package. Send coupon together with your card, professional letterhead or other indication of your professional standing.

**VISIT OUR BOOTH
No. 59 at the Eighteenth
Annual Clinical Session of
the American College of
Physicians to be held April
16th to 20th at the Palmer
House, Chicago, Illinois**

OVALTINE

The Swiss Food-Drink
Manufactured under license in U. S. A.
according to original Swiss formula

**This offer is limited only to practicing
nurses, physicians and dentists**

THE WANDER COMPANY A.I.M. 3
180 No. Michigan Ave.
Chicago, Ill.

Please send me, without charge, a regular size package of OVALTINE. Evidence of my professional standing is enclosed.

Dr. _____

Address _____

City _____ State _____

Canadian subscribers should address coupons to
A. Wander, Limited, Elmwood Park,
Peterborough, Ontario.

Hospital Consultation and Advisory Service

The necessity for an annual audit of the business accounts of a hospital is generally recognized. More vitally important is an equally thorough analysis of the quality of professional service rendered and the degree of adherence to universally accepted standards. A complete survey embraces a study of all phases of a hospital's activities.

Office of
WILLIAM HENRY WALSH, M.D.
612 North Michigan Avenue
CHICAGO

The WYATT CLINIC

for

Chronic Arthritis

3

TUCSON, ARIZONA

GRADWOHL SCHOOL OF LABORATORY TECHNIQUE

Attention of Fellows of the American College of Physicians is called to our exhibition at the forthcoming meeting in Chicago.

As in the past, we shall endeavor to display methods used by this institution in teaching. On this occasion, among other things, a very unique display box will be shown illustrating the normal blood development according to the Schilling methods.

This box has been reproduced on a small scale in a chart form, which will be offered for sale at \$2.00 per chart. The chart is in natural colors, is 8 x 10 inches, mounted on heavy cardboard and shows thirty different blood cells together with an explanation of the shift of the neutrophils as seen in infection.

Other specimens and microscopical views will be shown, illustrating hematological studies. Our booth is No. 61.

Gradwohl School of Laboratory Technique

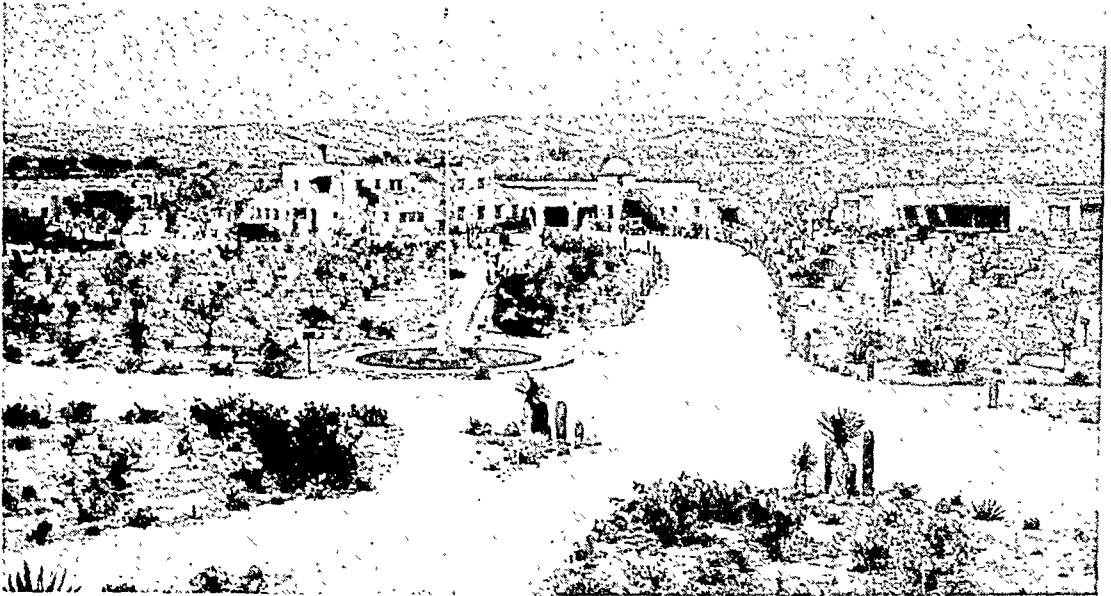
3514 LUCAS AVENUE

ST. LOUIS, MISSOURI

R. B. H. Gradwohl, M.D., *Director*

The Desert Sanatorium and Institute of Research

Tucson, Arizona



Altitude 2,600 feet

Entering upon its eighth season, this well-known Institution affords the facilities of modern diagnosis and treatment under unexcelled climatic conditions. Its appointments represent the acme of attractiveness, comfort and convenience. Not a hospital for the treatment of pulmonary tuberculosis, it aims at the utmost perfection of diagnosis and treatment of every condition that may be benefited by a warm, dry, sunny climate of desert type, such as chronic arthritis, sinusitis, nontuberculous pulmonary and upper respiratory complaints, arterial hypertension, cardiorenal insufficiency, etc.

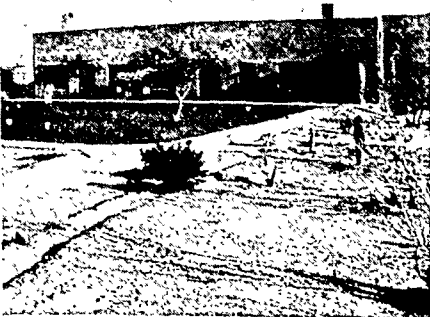
ALLEN K. KRAUSE, M.D., *Director*

W. PAUL HOLBROOK, M.D., *Physician-in-Chief*

VIVIAN TAPPAN, M.D., *In Charge of Pediatrics*

MAX PINNER, M.D., *Director of Laboratories*

CHARLES W. MILLS, M.D., *In Charge of Visiting Staff*



Recreation Centre



Out-Patient Clinic

For RATES AND OTHER INFORMATION

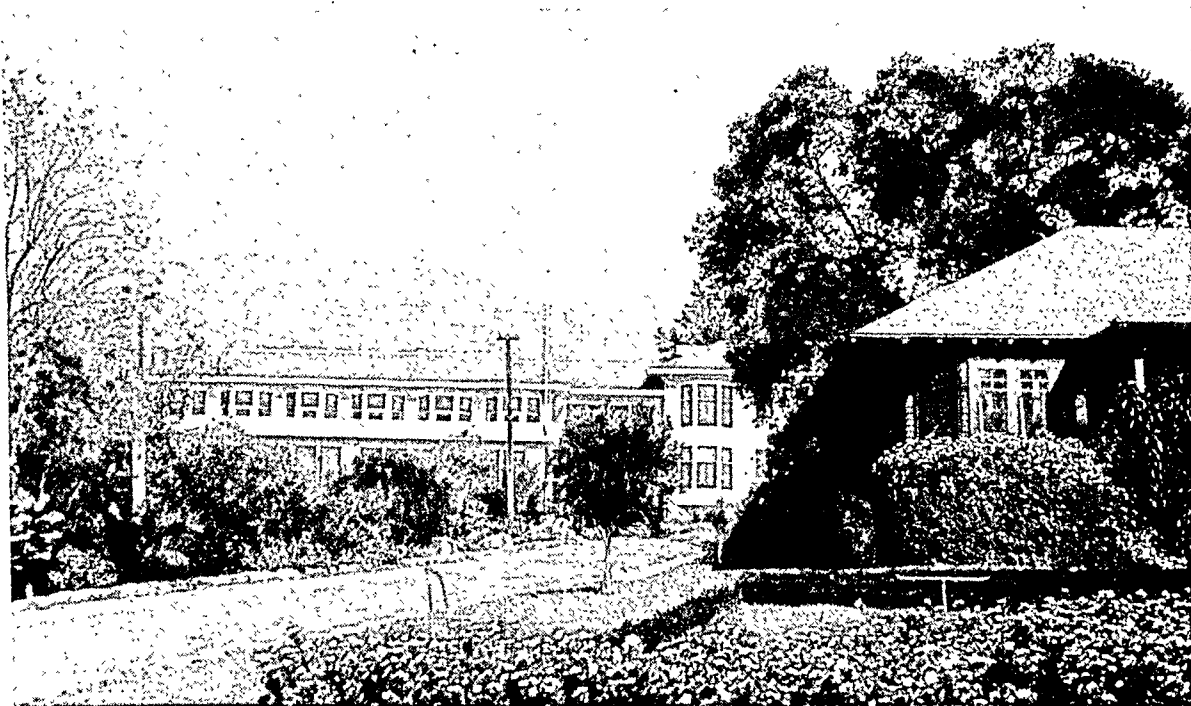
WRITE FOR BOOKLET

Address *Secretary, Desert Sanatorium*
Tucson, Arizona

Please Mention this Journal when writing to Advertisers

THE POTTENGER SANATORIUM AND CLINIC FOR DISEASES OF THE CHEST

Monrovia, California



THIRTY YEARS' EXPERIENCE IN THE TREATMENT OF TUBERCULOSIS

LOCATION

Sixteen miles east of Los Angeles. In the foothills of the Sierra Madre Mountains, at an elevation of 1000 feet. On the main line of Santa Fe Railway. Connected with Los Angeles by interurban railway and splendid boulevards.

ENVIRONS

The grounds consist of a beautiful park of forty acres, in which are found a variety of native Live Oaks, subtropical trees and plants, and a profusion of beautiful shrubs and flowers. Many winding walks and nooks of exquisite beauty add to its attractiveness. When on exercise, patients also enjoy the beautiful trails in the adjoining canyons and mountains.

MEDICAL CARE

Competent resident staff. Examinations for comparison every six weeks. Close medical supervision. Individual needs and problems receive personal attention.

THERAPEUTIC CARE

Fads are not followed, but an endeavor is made to give patients the amount of rest and exercise suited to their individual needs; the benefits of a liberal and adequate diet; such tonic measures as will increase their resistance, and other measures that will help them overcome any disturbing symptoms or complications that may arise. Heliotherapy, tuberculin, pneumothorax and surgery employed whenever indicated.

Weekly rates from \$25.00 up, including medical attention, medicines (except expensive remedies) and general nursing. Extra charge for operative measures (except pneumothorax).

DIAGNOSTIC CLINIC

A diagnostic clinic is maintained for the study of all diseases of the chest.

F. M. POTTENGER, M.D., Medical Director

For Particulars Address

THE POTTENGER SANATORIUM, Monrovia, California

THE ANALYSIS SHOWS

THE VALUABLE ALKALINE CHARACTER OF

VICHY CÉLESTINS

Natural Mineral Water

INDICATIONS

In stomach and
liver affections
and digestive disorders
in general;
in gout, arthritis
associated with uric
acidemia, uricemia,
and nephrolithiasis of
uric acid origin.



BOTTLED
AT THE SPRING
VICHY, FRANCE

ANALYSIS (GRAMS PER LITER)

Sodium bicarbonate	3.3090
Potassium bicarbonate	0.2490
Lithium bicarbonate	0.0281
Calcium bicarbonate	0.7400
Magnesium bicarbonate	0.1016
Ferrous bicarbonate	0.0012
Sodium chloride	0.3830
Sodium sulphate	0.2430
Silica	0.0300
Sodium arseniate, Phosphate and nitrate	} present

Brochure with Therapeutic Data and Medical Bibliography
sent on request.

Sole United States Agents, American Agency of French Vichy, Inc., 503 Fifth Ave., New York

NEW LEA & FEBIGER BOOKS

NEW WORK

JUST READY

ALLERGY IN GENERAL PRACTICE

By **SAMUEL M. FEINBERG, M.D., F.A.C.P.**

Assistant Professor of Medicine and Attending Physician in Asthma and Hay Fever Clinic, Northwestern University Medical School; Professor of Medicine in the Cook County Graduate School of Medicine; Attending Physician, Cook County Hospital, Chicago, Ill.

Octavo, 339 pages, illustrated with 23 engravings and a colored plate. Cloth, \$4.50, net

This book is unique among texts on allergy, in that it restricts itself to material that can be put into immediate use by the general practitioner and avoids the experimental and the theoretical. It presents asthma from the standpoint of symptoms, pathology, etiology, diagnosis and treatment; covers the hay fever problem with definite instructions concerning its management and treats all other allergic diseases without repetition. It is non-technical and non-speculative. Its case histories covering periods of weeks, months and even years include physical findings, tests and their interpretation, and the steps in treatment. Its section on plants and pollens is so organized that the physician can identify readily the problems of his own locality.

NEW (2nd) EDITION

JUST READY

LABORATORY MEDICINE

A Guide for Students and Practitioners

By **DANIEL NICHOLSON, M.D.**

Member of the Royal College of Physicians, London; Assistant Professor of Pathology, University of Manitoba; Assistant in Pathology, Winnipeg General Hospital, Winnipeg, Canada

Octavo, 566 pages, illustrated with 124 engravings and 3 colored plates. Cloth, \$6.50, net

The first edition of this useful work was exhausted within a very short time. Nevertheless, the many advances in this field have necessitated this thoroughly revised and much enlarged second edition, providing fully detailed information on the indications, methods and interpretations of diagnostic tests. The more highly technical procedures usually performed for the doctor by the laboratory are outlined, and the principles and the interpretations given. The book includes the indications for each test, a description of the technique and the interpretation showing the justifiable conclusions. Many tests most useful in diagnosis which may be performed with limited facilities are included. Special short chapters have been devoted to blood examinations, urinalyses, sputum examinations and similar topics. There is an abundance of supplementary material dealing with laboratory maintenance and operation.

NEW (3rd) EDITION

JUST READY

HYPERTENSION AND NEPHRITIS

By **ARTHUR M. FISHBERG, M.D.**

Associate Physician to Beth Israel Hospital; Associate in Medicine, Mount Sinai Hospital, New York City

Octavo, 668 pages, illustrated with 39 engravings and a colored plate. Cloth, \$6.50, net

This important work passed through two editions within a very short time. The extensive advances in this field have, however, necessitated the revision of almost every chapter in the preparation of this third edition. The differentiation of renal and extrarenal factors, so important for rational treatment, has been stressed throughout. As in the previous edition, the particular needs of the family physician whose laboratory facilities are generally limited have been constantly borne in mind. Diagnosis by clinical methods has been stressed and particular attention has been given to symptomatology so fundamental to accurate diagnosis. The treatment recommended is by simple dietetic measures which can be carried out in the home under the physician's direction. No book in our language covers this important subject so completely and so thoroughly.

LEA & FEBIGER

Please send me books checked:

☐ Feinberg's Allergy - - - - \$4.50 ☐ Fishberg's Hypertension - - \$6.50
☐ Nicholson's Laboratory Med. - 6.50 ☐ New Catalogue

Name _____

(A. of I. M. 5-34)

Address _____

600 Washington Square
PHILADELPHIA, PA.





SOME OUTSTANDING MACMILLAN books
to be published this Spring and
Summer.

Place your order now

THE MEDICAL AND ORTHOPAEDIC MANAGEMENT OF CHRONIC ARTHRITIS

A practical exposition of the subject of chronic arthritis of particular interest to internists, general practitioners and orthopaedic surgeons. The authors feel that chronic arthritis is largely a preventable and curable disease and that current knowledge of the nature of the disease and of measures necessary to combat it is not as generally diffused throughout the medical profession as it should be.

RALPH PEMBERTON,
M.S., M.D., F.A.C.P., Pro-
fessor of Medicine, Gradu-
ate School of Medicine, Uni-
versity of Pennsylvania, etc.

ROBERT B. OSGOOD,
A.B., M.D., F.A.C.S., John
Ball and Buckminster Brown
Professor Emeritus of Or-
thopaedic Surgery, Harvard
Medical School, etc.

Probable price \$5.00

TUMORS OF THE FEMALE PELVIC ORGANS

A survey of the present knowledge of the various tumors both benign and malignant that occur in the female pelvic organs. All common and many rare types are illustrated and their proper treatment outlined.

JOE VINCENT MEIGS,
M.D., F.A.C.S., Instructor in
Surgery, Harvard Medical
School, etc.

Probable price \$9.00

DISEASES PECULIAR TO CIVILIZED MAN

Written from its embryological, physiological, clinical and therapeutic aspects, it presents the theme that certain diseases, such as neurocirculatory asthenia, hyperthyroidism, peptic ulcer, diabetes and epilepsy, are related and result from the tension of highly civilized life.

GEORGE CRILE, M.D.,
Director, Cleveland Clinic;
Professor Emeritus of Sur-
gery, Western Reserve Uni-
versity.

Probable price \$5.00

The Macmillan Company, Medical Dept.
60 Fifth Avenue, New York City

Please send information on:

.....
.....
.....
.....

Name

Address

City State

Please Mention this Journal when writing to Advertisers

*Definite dosage
Ease of administration
Sensible economy*



Each pill contains 0.1 gram (1½ grains) of physiologically tested digitalis leaves. The finished pills, too, are biologically assayed, thus giving re-assurance of their activity.

Each pill represents 15 minims of the U. S. P. tincture and permits of more accurate dosage than do liquids, as drops may vary in size.

These pills contain digitalis in its completeness and not any separated or extracted part of it, therefore present the entire therapy of this valuable drug.

Physician's trial size package and literature sent free upon request.

DAVIES, ROSE & CO., Ltd.

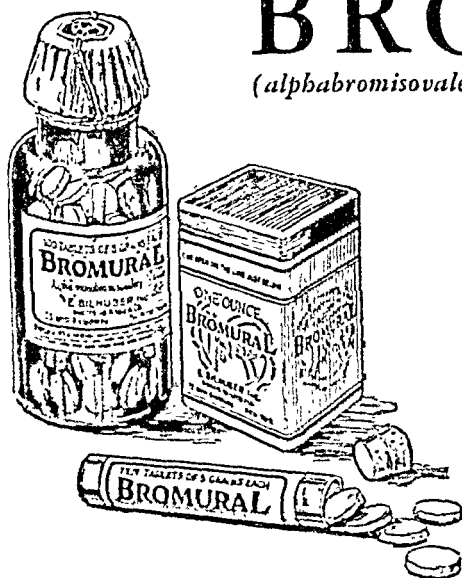
Pharmaceutical Manufacturers, - BOSTON, MASS. D8

As a routine sedative

BROMURAL

(alphabromisovalerylurea)

Council Accepted



Useful as a stronger sedative than the bromides, or where a mild and quickly acting somnifacient is in place. It is not a barbiturate.

DOSE: As a sedative, 5 grains (or 1 tablet) several times a day. In Sleeplessness, 10 to 20 grains.

...

Samples and literature from

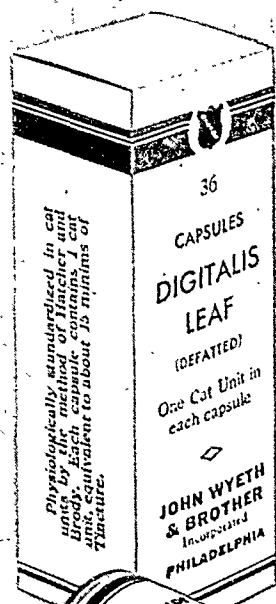
BILHUBER-KNOLL CORP., 154 Ogden Ave., Jersey City, N. J.

Replacing the Medicine Dropper

In digitalis medication, where accuracy of dosage is essential, the use of the medicine dropper by the patient for measuring dosage is often inadvisable. You will thus appreciate Wyeth's Capsules Digitalis Leaf (Defatted) for accuracy of dosage, convenience and uniformity. They offer several decided advantages, regardless of individual preferences as to methods of standardization:

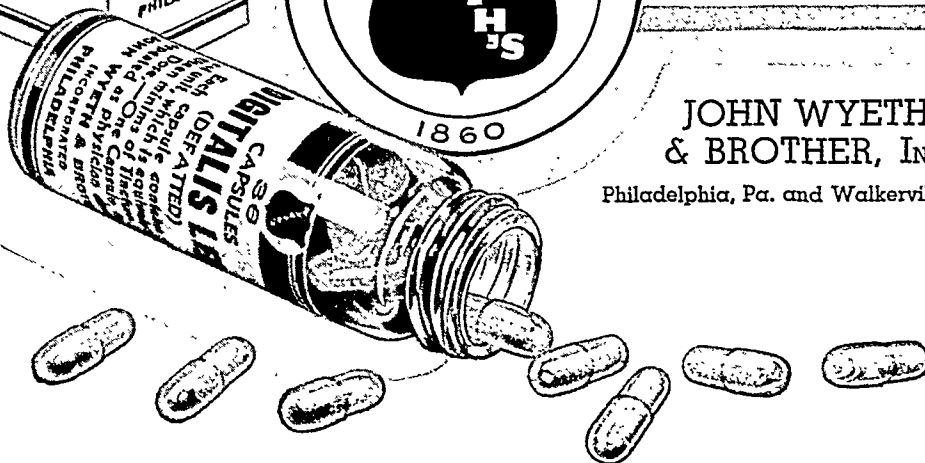
1. Dependable activity of the drug.
2. Unvarying quantity of digitalis in each capsule.
3. Each capsule represents: 15 minims of Tincture Digitalis U. S. P. or 1 Cat Unit (Hatcher and Brody).
4. Doubly Standardized—Assayed by both the U. S. P. Frog Method and the Cat Method of Hatcher and Brody.
5. Convenient—Obviates discrepancies between minims and drops, and avoids the use of household measuring devices.

Supplied in vials of 36 capsules (sufficient for average digitalization).



**JOHN WYETH
& BROTHER, INC.**

Philadelphia, Pa. and Walkerville, Ont.



Please Mention this Journal when writing to Advertisers

For **20** Years

HAY FEVER

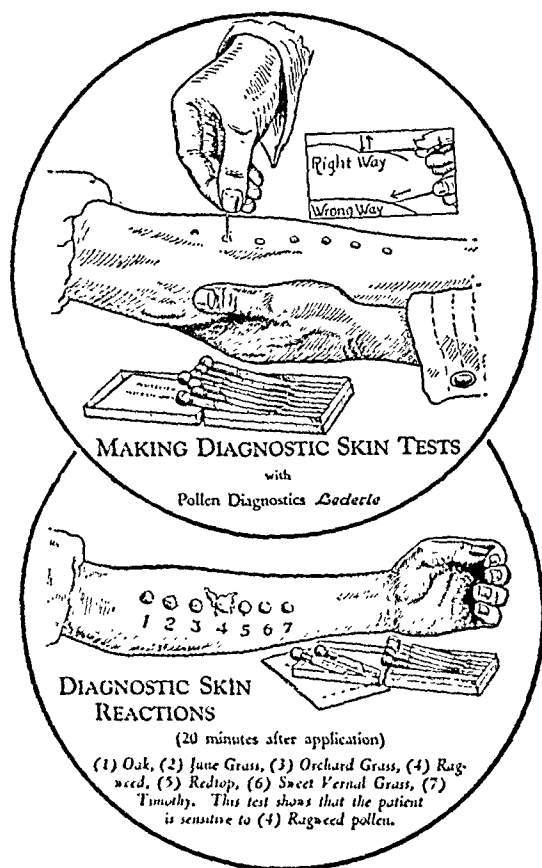
has been prevented

*in thousands of cases
with*

Pollen Antigen

Lederle

INTRODUCED BY LEDERLE LABORATORIES IN 1914



DIAGNOSIS OF HAY FEVER

With the Lederle Diagnostic Pollen Tests the diagnosis may be made in your office or in the patient's home.

A positive reaction occurring with a pollen to which the patient is known to be exposed when he is having Hay Fever indicates the Pollen Antigen to be used in desensitizing the patient.

The test is easily performed, accurate and safe.

GLYCEROLATED POLLEN ANTIGENS in stable and standardized solutions provide the general practitioner with a means for the scientific treatment of his Hay Fever patients. Each year has added evidence to the value of these solutions in the prevention and relief from symptoms of Hay Fever and each year an increasing number of physicians have familiarized themselves with the Hay Fever problem and are relieving their patients' attacks.

Literature upon request.

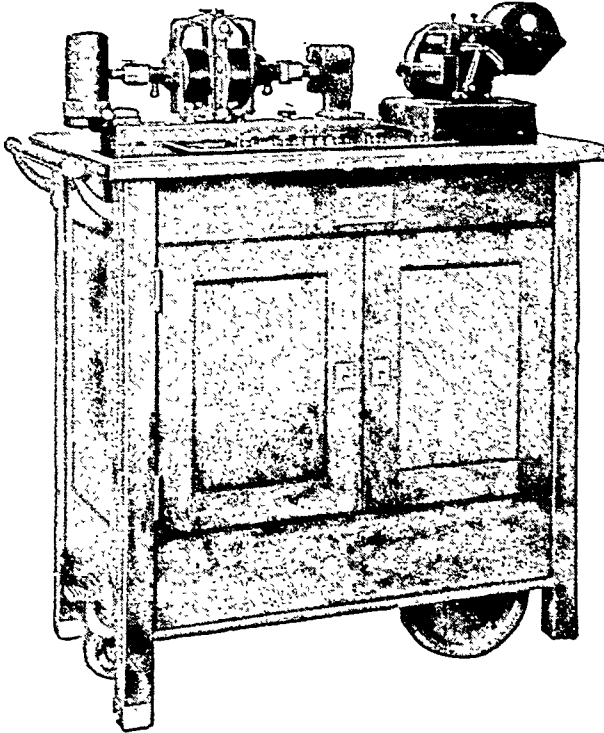
LEDERLE LABORATORIES
INCORPORATED

511 FIFTH AVENUE, NEW YORK

HINDLE

"ALL-ELECTRIC"

ELECTROCARDIOGRAPH



The new All-Electric Models are made in Stationary, Mobile, and Portable types for hospitals, clinics and private offices.

From time to time, substitutes are suggested for the Einthoven String Galvanometer as the current responsive element of the Electrocardiograph. It is well known that the String Galvanometer has sufficient sensitivity to directly record heart action-currents without amplification and is sufficiently robust for all demands. It is, therefore, a fundamental standard . . . and is recognized at such the world over.

"Hindle" Electrocardiographs possess this inherent sensitivity. They are therefore sound in principle, simple in

construction, and give unquestioned results and years of satisfactory performance. Through many steps of almost continuous development and simplification of the Electrocardiograph, the Cambridge Company has refused to tamper with fundamentals.

The art of Electrocardiography in the United States has been largely developed upon the "Hindle" Electrocardiograph and its installation list includes many of the most prominent Medical Schools, Hospitals, and Heart Specialists in this country.

CAMBRIDGE
INSTRUMENT CO INC

3732 Grand Central Terminal, New York City

"Pioneer Manufacturers of the Electrocardiograph"

Please Mention this Journal when writing to Advertisers

LIKE EXPELLING WATER ...from a Sponge



MOST diuretics act chiefly upon the kidneys and have but a limited influence on the dropsical tissue cells.

Salyrgan exercises a dual action: It liberates the fluid and salts from the colloid condition in which they exist in the tissue cells, thus facilitating the entrance of fluid into circulation, and also stimulates elimination by the kidneys. The effect of Salyrgan is rapidly developed. Frequently the urinary output is as much as 5000 cc. daily.

The field of indications for Salyrgan comprises especially marked types of cardiac and cardio-renal dropsy where a powerful diuretic is required. Its use in renal disease should be confined to the early stages of chronic nephritis and the nephroses. Favorable results have also been reported in hepatic ascites and Banti's disease.

Salyrgan (mercury salicylallylamide-o-acetate of sodium) is administered intramuscularly or intravenously in doses of 0.5 to 2 cc.

Supplied in ampules containing 1 cc. (boxes of 5) and 2 cc. (boxes of 10).

Send for literature outlining the experiences at prominent institutions with this potent diuretic.

SALYRGAN

Reg. U. S. Pat. Off. and Canada (Brand of MERSALYL)

H. A. METZ LABORATORIES, INC., 170 Varick Street, New York, N. Y.

224M

Please Mention this Journal when writing to Advertisers

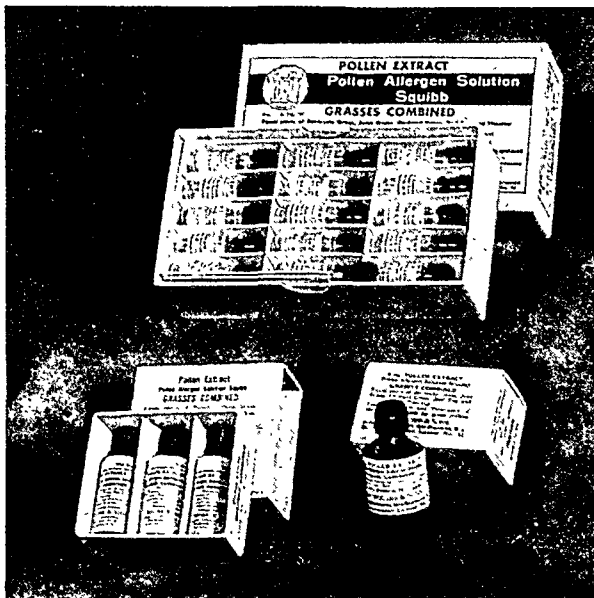


HIGH POTENCY

assures adequate treatment

SUCCESSFUL immunization against hay fever depends upon the desensitizing activity of the extract. It is advisable that treatment be commenced early enough (about six weeks prior to the expected onset of the attack) to permit the development of a high degree of desensitization before the season begins.

Squibb Pollen Allergen Solutions are glycerol-solutions of the antigenic proteins of pure native pollens and are standardized in terms of the protein nitrogen unit. They are prepared by methods which assure high potency, adequate stability and uniform dosage.



FOR DIAGNOSIS:

A large assortment of Pollen Allergen Solutions is available.

FOR TREATMENT:

5 cc. VIALS—An equally large assortment of Pollen Extracts is provided of uniform potency. 10,000 protein nitrogen units per cc. (equal approximately to 13,333 Noon pollen units).

THE 3-VIAL PACKAGE (grasses combined; ragweeds combined) for convenience and economy (39,000 protein nitrogen units, 52,000 Noon pollen units).

Enough material for 15 doses plus a generous excess. Permits unlimited flexibility of dosage. No dilution or mixing required.

THE 15-DOSE TREATMENT SET A (grasses combined; ragweeds combined) supplies a total of 16,000 protein nitrogen units as defined by Cooke and Stull (equal to 22,717 Noon pollen units).

TREATMENT SET D, which supplies five additional ampuls of Dose 15, increases the total protein nitrogen units to 41,000 (equal to 56,000 Noon pollen units).

For literature giving complete information, compact and simplified dosage schedules and pollen distribution, mail the coupon

E. R. SQUIBB & SONS
MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1838
NEW YORK

E. R. SQUIBB & SONS,
Professional Service Department,
4804 Squibb Building, New York

Please send me literature on the prophylaxis and treatment of hay fever.

Name

Street

City..... State.....



Thou driftest gently down the tides of sleep.—LONGFELLOW

ORTAL SODIUM

The New
BARBITURIC
HYPNOTIC

Ortal Sodium is accepted for N. N. R. by the Council on
Pharmacy and Chemistry of the American Medical Assn.

ORTAL SODIUM—the result of ten years
of research in the Parke-Davis laborator-
ies—is an effective rapidly-acting hypnotic; it
induces sound, restful sleep, so necessary in a
wide variety of physical and mental disorders.
Ortal Sodium has low toxicity, and its use is
free from unpleasant hang-over effect.

The effective hypnotic dose in most cases is
one or two capsules.

Samples to physicians on request.

*Supplied in
bottles of 25, 100
and 500 3-grain
capsules.*



Parke, Davis & Co. **DEPENDABLE MEDICATION
BASED ON SCIENTIFIC RESEARCH**

ONE HUNDRED YEARS LATER

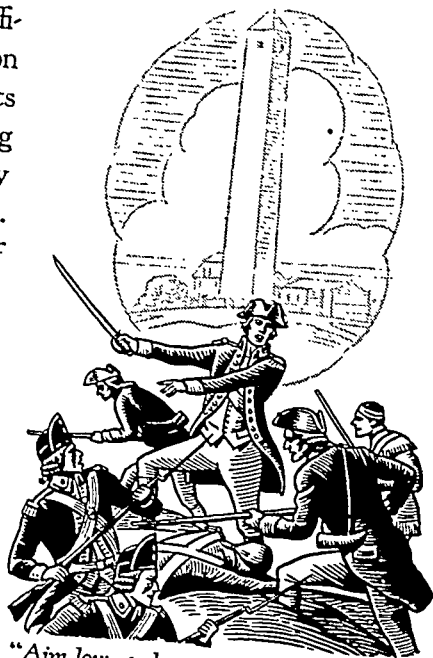
THE Centenary of the Battle of Bunker Hill was celebrated with great pomp and enthusiasm on June 17th, 1875. In that same year The Maltine Company was established and introduced its first product—Maltine With Cod Liver Oil.

In the 59 years since it was introduced to physicians and long before any one knew anything about vitamins, the medical profession held Maltine With Cod Liver Oil in high esteem because of its proved efficiency in the prevention and treatment of rickets as well as in the building of strength and bodily resistance against disease.

With the discovery of the various vitamins and when their identity and functions had become better known, The Maltine Company, with the assistance of nationally known scientists, began a systematic and exhaustive series of tests to discover the vitamin potency of Maltine With

Cod Liver Oil. These tests demonstrated, among other things, that this product is rich in four important vitamins—A, B, D and G. The B and G vitamins are supplied by the Maltine (70% of the total content)—a concentrated fluid extract of the nourishing elements of malted barley, wheat and oats. Vitamins A and D are provided by the 30% balance of vitamin-tested cod liver oil.

As authorities now favor the ingestion of vitamins as a group rather than as isolated vitamins, Maltine With Cod Liver Oil offers an ideal medium for group vitamin administration. Maltine With Cod Liver Oil is biologically standardized and guaranteed to contain four vitamins—A, B, D and G. When taken with orange or tomato juice, the fifth vitamin—C—is added. Biological report on request. The Maltine Company, 30 Vesey St., New York, N. Y.



"Aim low, and wait till you see the whites of their eyes." GEN. PUTNAM at Battle of Bunker Hill, June 17th, 1775.

This Trade-mark Identifies the Only Genuine

Maltine

Reg. U. S. Pat. Off.

WITH COD LIVER OIL—Introduced in 1875



Member NRA
We do our part

Maltine with Cod Liver Oil and Iron Iodide also available. This is identical with Maltine with Cod Liver Oil except that it contains two grains of freshly prepared iron iodide to each fluid ounce.

Please Mention this Journal when writing to Advertisers

Calcium Deficiencies IN TETANY

"**W**HEN all the facts of tetany are arrayed it is impossible to escape the impression that there is a fundamental relation between the various types," is the opinion of Peters and Van Slyke.¹

The disorder may take such forms as the spasmophilia of infancy, the tetany of pregnancy, the convulsions of uremia, postoperative tetany, parathyroid tetany, and that associated with osteomalacia.

Cantarow² finds that when serum calcium falls below 7 mg. per 100 c.c. symptoms of tetany are manifest.

Alfred Hess notes that tetany occurs "frequently, in fact generally, in a latent form."³ In view of this the physician must be on guard against tetany in those cases where there is likely to be a drain on the calcium stores, particularly during growth and in pregnancy and lactation. Considering that the average diet is probably lower in calcium than in any other chemical

element, the problem of increasing calcium intake through ordinary foods is difficult. Calcium salts, moreover, are not usually relished by the patient.

A larger intake of calcium alone is not effective, however, unless the body is able to utilize the added minerals. Moreover, tetany is marked by elevations of serum phosphorus, according to Collip.⁴ Thus the problem arises not only of increasing calcium concentration but also of maintaining the proper ratio between calcium and phosphorus. "Vitamin D, as is well known, has remarkable power to regulate calcium and phosphorus metabolism," McCollum observes.⁵

Alfred Hess declares increased calcium intake together with viosterol to be the treatment of choice in tetany.³ He adds the significant comment that in tetany viosterol is characterized by its rapid action, whereas cod liver oil, in infantile tetany at least, appears to act upon the concomitant ricketic condition rather than upon the tetany.

MEAD'S CEREAL*

Enriched with mineral and vitamin containing foods

SUPPLIES Calcium

Containing 0.22 Gm. Ca and 0.17 Gm. P per ounce, this delicious cereal is richer in these minerals than most principal foodstuffs. Two ounces supplies as much calcium as 12 ounces of fluid milk; and thus obviates the need for excessive quantities of liquid in the diet. It also makes good the iron and vitamin B deficiencies of milk.

MEAD'S VIOSTEROL

IN OIL 250 D

UTILIZES Calcium

Alfred Hess says of viosterol: "One of the distinctive characteristics of this remarkable substance is that it raises the level of either inorganic phosphorus or of calcium, depending on which is in low concentration in the blood or tissues."³ Uniformly potent, accurately assayed, Mead's Viosterol can be depended upon for good results in tetany.

¹⁻⁵ Bibliography on request.

MEAD JOHNSON & CO., Evansville, Ind., *Pioneers in Vitamin Research*

Please mention this advertisement when requesting samples of Mead Johnson products to cooperate in preventing their reaching unauthorized persons.

* Now also supplied in pre-cooked form, as PABLUM. Dried, ready to serve by simply stirring (with a fork) with water or milk, hot or cold. Completely prepared in the cereal bowl in a few moments.

Please Mention this Journal when writing to Advertisers

ANNALS OF INTERNAL MEDICINE

VOLUME 7

MAY, 1934

NUMBER 11

PERIARTERITIS NODOSA

A BRIEF REVIEW OF THE LITERATURE AND A REPORT OF ONE CASE *

By ARTHUR C. CURTIS, B.S., M.D., F.A.C.P., and ROBERT M. COFFEY,
M.D., *Ann Arbor, Michigan*

PERIARTERITIS nodosa is a primary vascular disease of moderate duration usually characterized by an insidious onset with mild fever, emaciation, weakness, fatigue, loss of weight, pains in the arms, legs, abdomen, and leukocytosis. The signs and symptoms frequently vary, depending upon the location of the arteries involved, and because of this Harbitz¹ has classified the disease into gastrointestinal, renal, neuro-muscular, cardiac, cerebral and cutaneous types. Though any one of these types may exist alone, various combinations are usually seen.

Periarteritis nodosa is rarely, if ever, diagnosed clinically. Biopsy, taken for some other purpose, may show its existence. Relatively few cases have been reported, though Strong² in his review of the literature in 1928 found 142, but only 21 of these were in English. Strong summarized the cases reported in English and added a case of his own. Since then 16 more cases have been reported in English and it is our purpose to review these and add another case which has many peculiar aspects both clinically and pathologically, and illustrates particularly the cutaneous and neuro-muscular aspects of the disease. Our case was diagnosed ante mortem.

CASE HISTORY

F. R., white, male, aged 47, was first admitted to the University Hospital May 19, 1931. He gave a history of cough, productive of purulent sputum, which had been present for two and one-half years. A diagnosis of bronchiectasis was made. Following a nasal polypectomy and submucous resection he was discharged. He was advised to take potassium iodide, and was given instructions in postural drainage. On this regimen he apparently improved.

The patient was again admitted to the University Hospital on August 18, 1932, at which time he complained of weakness of his extremities. He stated that six months before admission both ankles and feet had become swollen and painful. The pain was dull and aching in character, and had been present constantly with occasional sharp exacerbations. He had remained in bed for three months and during this time

* Received for publication March 20, 1934.

the swelling of his ankles disappeared and reappeared several times, but the pain had persisted constantly. Two months before admission his right elbow had become ulcerated. On one occasion he had noticed numbness and tingling in both hands and swelling and pain in both wrists. The next day he had found that he was unable to move the fingers in either hand. His appetite had been poor and he had lost 40 pounds in weight in the six months before admission. He had recently had some difficulty in swallowing. The past history was essentially negative except for asthma.

Physical Examination. Showed the patient to be an emaciated, pale, adult male with evidence of marked loss of weight and generalized muscular atrophy. He did not appear to be acutely ill. The head, eyes, ears, nose, and neck were negative. The mouth was edentulous. The heart was not enlarged, no murmurs were heard, the rhythm was regular, the rate 92 beats per minute, and the blood pressure 110 systolic and 80 diastolic. The abdomen was somewhat distended and the percussion note was tympanitic. No organs, masses, or points of tenderness were palpable. All muscles of the extremities were markedly atrophic. Those of the shoulder girdle and the small muscles of the hands showed this most plainly. The patient was unable to flex his fingers, and was unable to hold a fork in his hand. The grip in both hands was weak, but more so on the right. The left biceps reflex was not obtained. The left triceps jerk was normal. The reflexes of the right arm were not obtained because of a partial ankylosis and the decubital ulcer on the right elbow. The abdominal reflexes were active in all four quadrants. The knee jerks were equally hyperactive. The Achilles jerks were normal. Plantar stimulation gave no movement of the toes on the right and extension of the toes on the left. Vibratory sensation was diminished in both ankles; normal in the knees and hips; absent in the wrists.

Laboratory Findings. The urine was acid in reaction. The specific gravity was 1.020. No albumin or sugar was present. There were 15 to 20 white blood cells and three granular casts per high power field. The blood on admission showed 66 per cent hemoglobin and 3,650,000 red blood cells. The leukocyte count was 5,100 and a differential smear showed 66 per cent polymorphonuclears, 9 per cent eosinophiles, 22 per cent lymphocytes and 3 per cent monocytes. The stool was negative. The Kahn reaction was negative. The spinal fluid Kahn, colloidal gold, and gum mastic reactions were negative. The urine creatinine was 1.11 grams per liter. The urine creatine was 0.91 grams per liter, and the blood creatinine 1.4 mg. per 100 c.c. The blood non-protein nitrogen was normal and the blood culture was negative. The stool culture was negative and the sputum showed no acid fast bacilli. Table 1 shows subsequent blood examinations.

A roentgen-ray of the chest on September 6, 1932 was negative, and on November 11, 1932 it showed chronic recurrent upper respiratory infection, possibly pneumonitis. A roentgenogram of the esophagus taken on November 23, 1932 was negative. A roentgen-ray of the chest on December 16, 1932 showed a mild widening of the aortic arch but no gross cardiac enlargement.

Electrocardiograms taken on November 2, 1932, and November 29, 1932 were negative. An electrocardiogram taken on December 17, 1932 was interpreted by Dr. Frank N. Wilson as follows: "The T-waves are inverted in Leads II and III. There is some change in the form of the electrocardiogram since the first one was taken. These changes are of a minor kind, but suggest that some changes have occurred in the heart." An electrocardiogram on January 14, 1933 was interpreted as follows: "There are flat T-waves in Leads I and II. In Lead III the T-waves are slightly inverted. The curves are not definitely abnormal and are similar to those taken previously."

Course in the Hospital. The patient was first admitted on the medical service of the University Hospital, August 17, 1932. For the most part the temperature, pulse, and respirations were normal except for occasional rises in temperature to 100° F.,

the causes of which were not evident. The diagnoses of both multiple neuritis and progressive muscular dystrophy were considered and the patient was transferred to the neurological service. A biopsy of the decubital ulcer of the right elbow was taken, followed by surgical closure of the wound. Microscopical examination showed it to be a chronic ulcer with a vascular base. On September 14, 1932, the patient was discharged from the hospital. He returned on October 4, 1932, and no improvement in his condition was noted. He had continued to have pain in the hands, arms and legs. A sinus had formed in his right elbow and it continued to drain. There was considerable edema of the right hand and forearm following the operation. On his return he was admitted to the surgical service for further treatment of the draining sinus. The cause of the edema of the hands and feet was not evident, so he was referred to the medical department where routine blood studies were done. These showed 59 per cent hemoglobin, 3,160,000 red blood cells, 18,300 white blood cells of which 63 per cent were eosinophiles. In view of this marked eosinophilia and the pain in the extremities the diagnosis of trichiniasis was seriously considered. A biopsy of the calf muscle was taken. The pathological report was: "Extensive atrophy of the voluntary muscle with a peculiar interstitial myositis. No trichinae were found. There is a heavy eosinophile infiltration which is chiefly perivascular. Many of the small blood vessels show organizing thrombi and proliferative changes in the vessel wall together with destructive lesions and the formation of small aneurysms. Many of these lesions bear a close resemblance to periarteritis nodosa." (Figures 1a, 1b, 1c.)

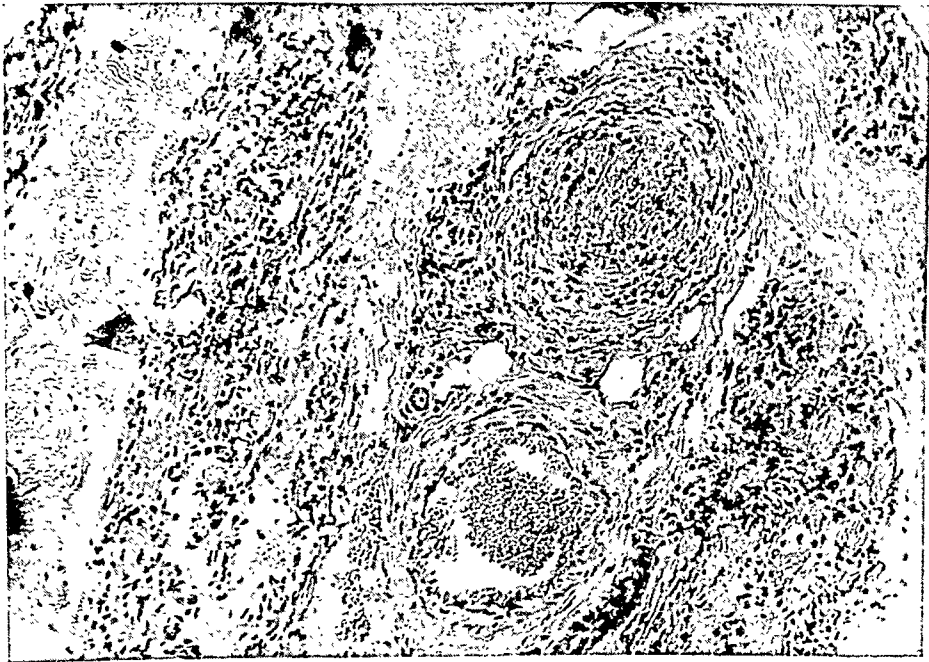


FIG. 1a. A section of biopsy material from a calf muscle showing extensive atrophy of the voluntary muscle with a peculiar interstitial myositis. There is a heavy eosinophile infiltration which is chiefly perivascular. Many of the smaller blood vessels show organizing thrombi and proliferative changes in the vessel walls.

In view of this report the patient was transferred back to the medical service on November 2, 1932, and physical examination was found to be essentially the same as previously reported, but there was edema of the ankles up to the knees and the decubital ulcer of the right elbow was partially healed. From then until the time of the patient's

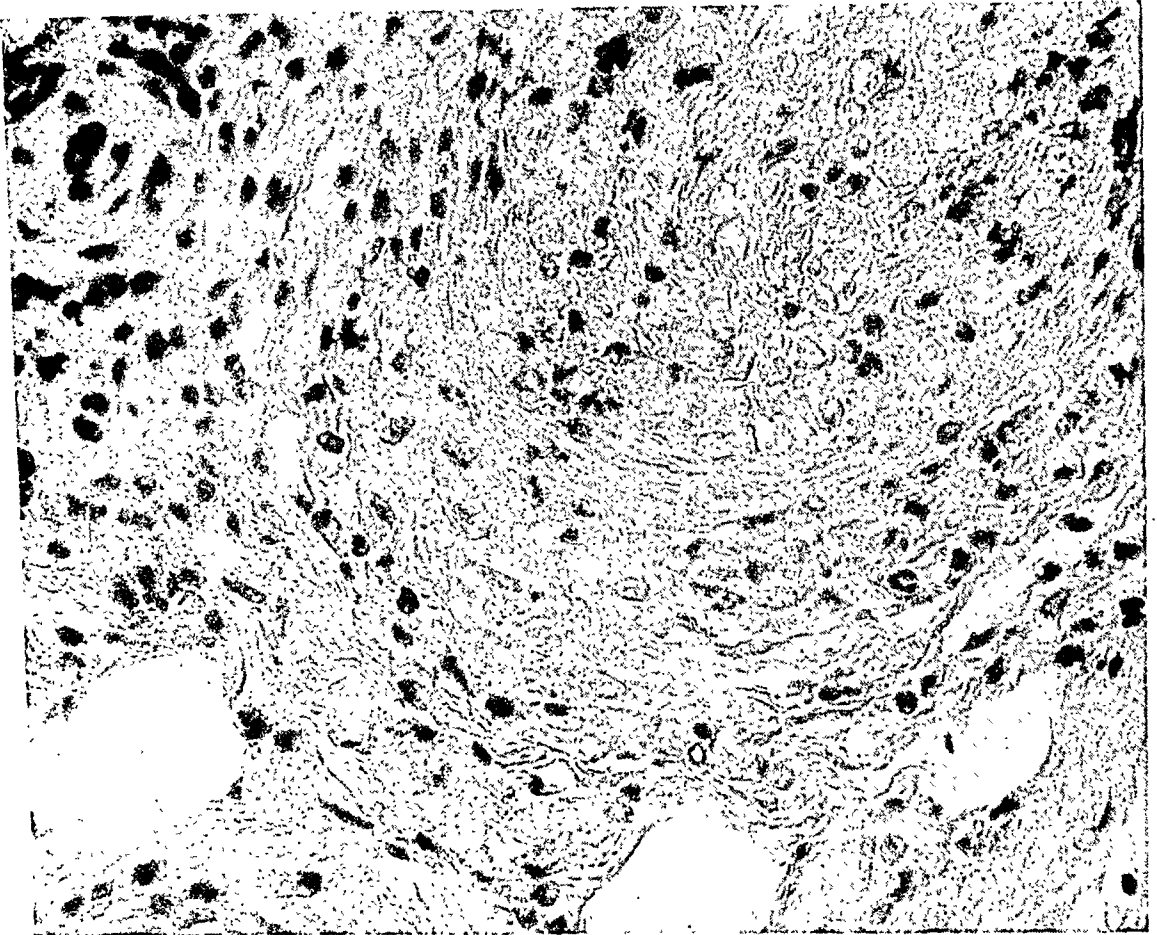


FIG. 1b. Same as figure 1a, high power. This section shows part of an organizing thrombus in an occluded vessel. Note the perivascular infiltration and the presence of many eosinophiles.

death, he had a marked eosinophilia and some elevation of his leukocyte count. (Table 1.) He was treated symptomatically. His weight remained constant at 47 kilograms. At times his appetite was good but, for the most part, he had marked anorexia. On December 3, 1932, he was discharged.

On December 7, 1932, he returned because of an attack of severe pain in the epigastrium and marked tenderness on very light palpation in this region. An electrocardiogram showed some changes, but still no marked abnormality. The patient was given a course of six injections of neoarsphenamine with no improvement. He was

TABLE I

Date	R.B.C.	W.B.C.	Hgb.	P.M.N.	Bas.	Eos.	Lymph.	Mono.
Aug. 17, 1932	3,650,000	5,100	66%	66	—	9	22	3
Oct. 20, 1932	3,160,000	18,300	59%	23	1	63	11	2
Oct. 27, 1932	2,820,000	12,200	57%	20	1	69	8	2
Nov. 2, 1932	3,610,000	11,450	64%	44	1	51	4	—
Nov. 19, 1932	3,150,000	12,600	61%	34	—	62	3	1
Nov. 22, 1932	3,280,000	11,900	65%	25	—	71	1	3
Dec. 7, 1932	3,760,000	19,900	65%	19	1	77	2	1
Jan. 5, 1933	3,110,000	13,100	62%	17	1	66	13	3
Jan. 17, 1933	2,650,000	14,150	56%	—	—	53	10	8

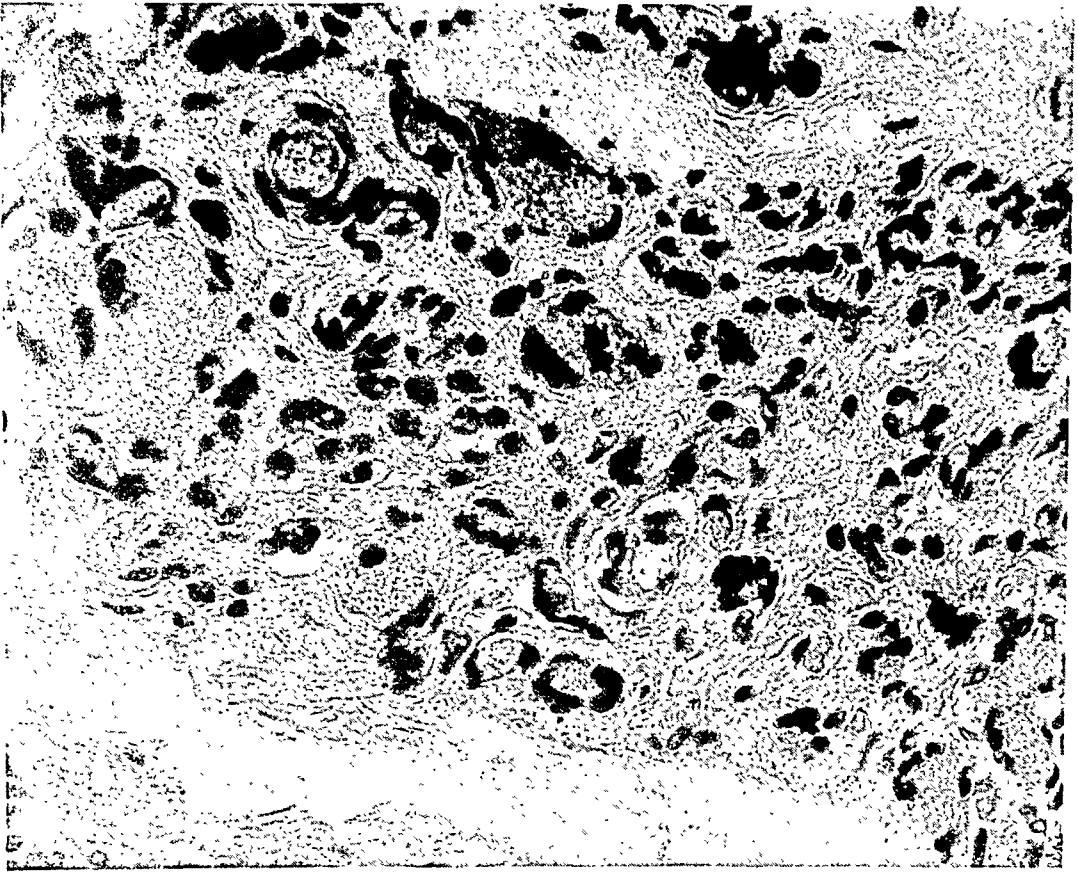


FIG. 1c. Same as figure 1a, high power. Showing a marked muscular atrophy and interstitial myositis. Cellular infiltration containing many eosinophiles is also seen here.

again discharged on January 24, 1933, and returned to the hospital on January 29, 1933.

His condition was unchanged until four days previous to his return when he developed a cough, productive of thick, green sputum. The physical examination at this time showed a marked expiratory grunt. His respirations were 29 per minute. The temperature was 101.6° F. The pulse rate was 96 per minute. The heart was negative. There were heard, on auscultation, diffuse, scattered râles over both lung fields; but these were most marked at the right base and in the interscapular region. The patient became delirious, his temperature rose to 102.8° F., and on January 31, 1933, he died.

The clinical diagnosis was periarteritis nodosa, neuro-dermatomyositis, broncho-pneumonia, secondary anemia.

Postmortem Findings. The body was that of a greatly emaciated adult male. There was marked atrophy of all of the skeletal muscles and marked edema of the feet. A partially healed decubital ulcer was found on the right elbow. Grossly all organs were negative with the exception of the lungs and heart.

The former showed changes characteristic of purulent bronchitis and broncho-pneumonia; the latter a vegetative endocarditis of the mitral valve flaps.

Microscopically, the spinal cord showed some congestion and slight edema of the inner meninges and moderate edema of the cord substance. There was early post-mortem myelinosis.

The brain showed congestion and slight edema of the meninges and brain substance. The vascular and interstitial changes found elsewhere in the body were not in evidence in the cerebral vessels or cerebral substance.

In the heart the smaller arteries and arterioles in the subepicardial tissues showed in many instances a perivascular infiltration rich in eosinophiles and a fibrous tissue increase in the adventitia. There was marked obliterative intimitis with reduction of lumina. (Figure 2.) There was atrophy of the myocardium. Multiple small

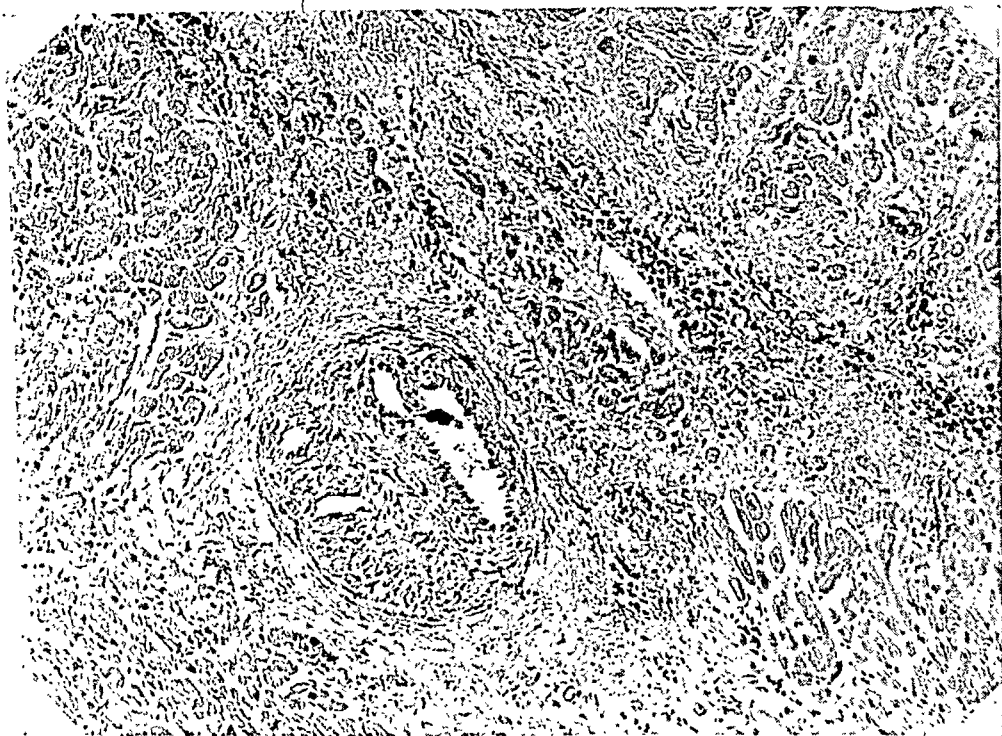


FIG. 2. Section of the heart showing a branch of one of the coronary arteries. There is a fibrous increase in the adventitia and a reduction of the lumen of the vessel by obliterative intimitis, with subsequent thrombosis, organization and canalization. Interstitial fibrosis and atrophy of the heart muscle are easily seen.

anemic infarctions in various stages of fibrosis were found in the myocardium, and were considered to be the result of arteriolar occlusion. There was hyaline thickening of the mitral valve flaps with organizing fibrinous vegetations present. The larger coronary branches were proportionately less involved than the smaller ones. The aneurysmal dilatations and nodosities so common in periarteritis nodosa were not found. In those instances in which evidence of interruption of the continuity of vessel walls was found, the defects had been filled in by young connective tissue without aneurysmal yielding. The aorta showed small eosinophilic perivascular infiltrations in the adventitia with obliterative changes of the type described elsewhere.

The lungs showed an acute exacerbation of chronic passive congestion. There was widespread acute purulent bronchitis and bronchopneumonia. The inflammatory exudate was unusually rich in eosinophiles. Some of the medium sized and larger bronchi showed hyaline thickening of the basement membrane and the formation of a tough mucin. There were irregular dilatations of the lumina of the bronchi and eosinophilic infiltrations of the walls, which were considered to be the changes found in bronchial asthma. One small completely organized embolus was seen. Patchy emphysema was present.

The same type of vascular change was found in the larynx, small arteries of the thyroid, esophagus, diaphragm, appendix, small intestines, stomach, pancreas, retroperitoneal arteries, muscles, skin, and the vessels accompanying the peripheral nerves. (Figures 3, 4 and 5.) The prostate gland, seminal vesicles, and urinary bladder also showed these arterial changes.

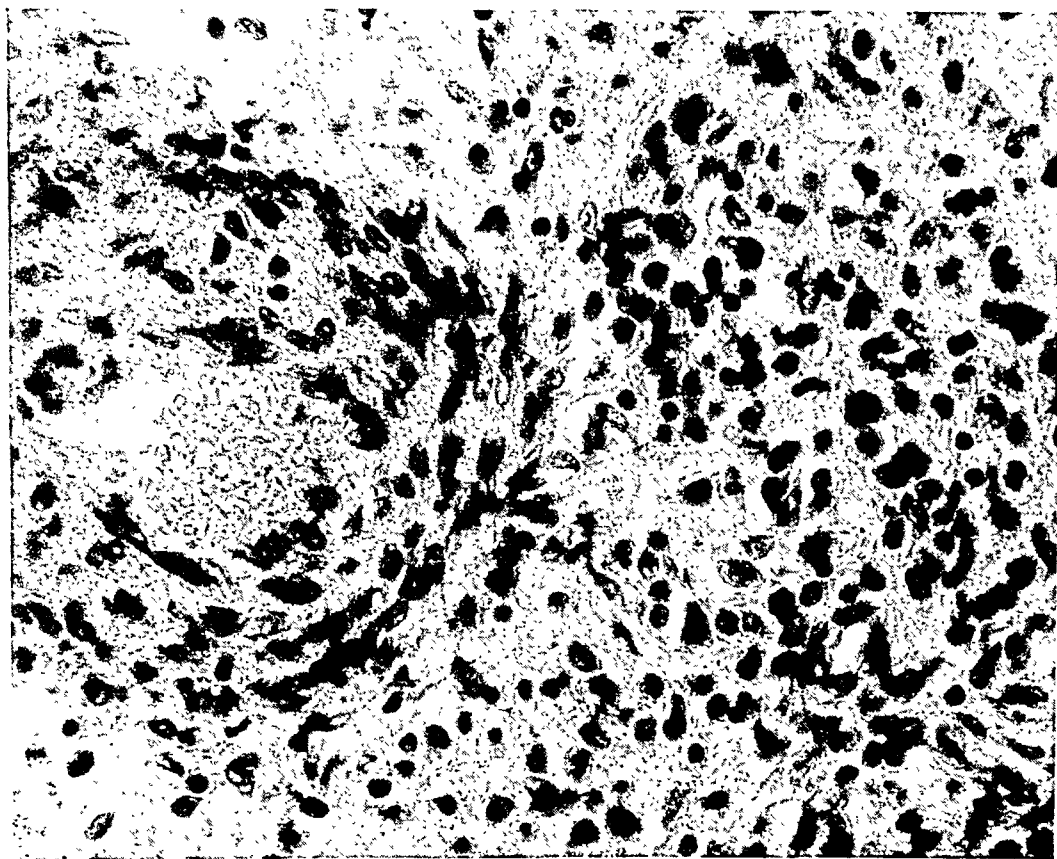


FIG. 3. High power, showing one of the smaller arteries with a fibrous increase in the adventitia and proliferative changes in the intima. There is a marked perivascular infiltration composed largely of eosinophiles.

The kidneys showed marked obliterative changes in the smaller arteries and arterioles. The outer portion of the cortex showed a confluent arteriolar, nephrocirrhosis with atrophy of the parenchymatous elements, increased stroma, and cellular infiltration in which there were many eosinophiles. (Figure 6.) There were hyaline and blood cell casts. The left ureter showed marked vascular changes in the walls with heavy eosinophilic infiltration at which point there was necrosis of a portion of the wall and ulceration of the mucosa with deposition of lime salts. The right ureter was negative.

DISCUSSION

The outstanding symptoms of this case were pain in the arms and legs, anorexia, loss of weight, nausea, and weakness. The most striking physical findings were the emaciation, generalized atrophy, and edema of the hands and feet. The points of interest in the laboratory findings were the second-



FIG. 4. A nerve trunk showing arterial changes of the same type as seen elsewhere with secondary edema of the nerves and nerve sheaths. There is no active neuritis.

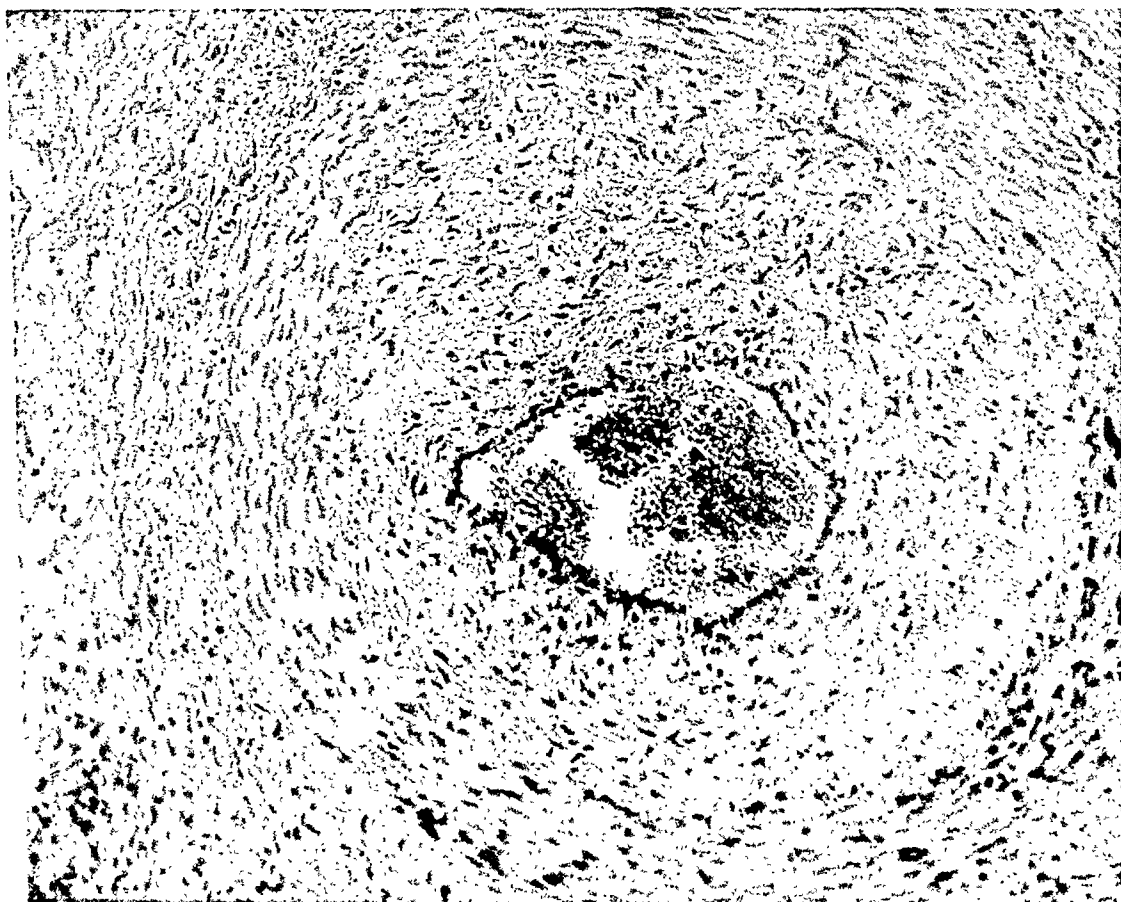


FIG. 5. High power. A section from a medium sized artery showing fibrotic changes in the adventitia and a proliferative intimitis. There is a mild perivascular cellular infiltration.

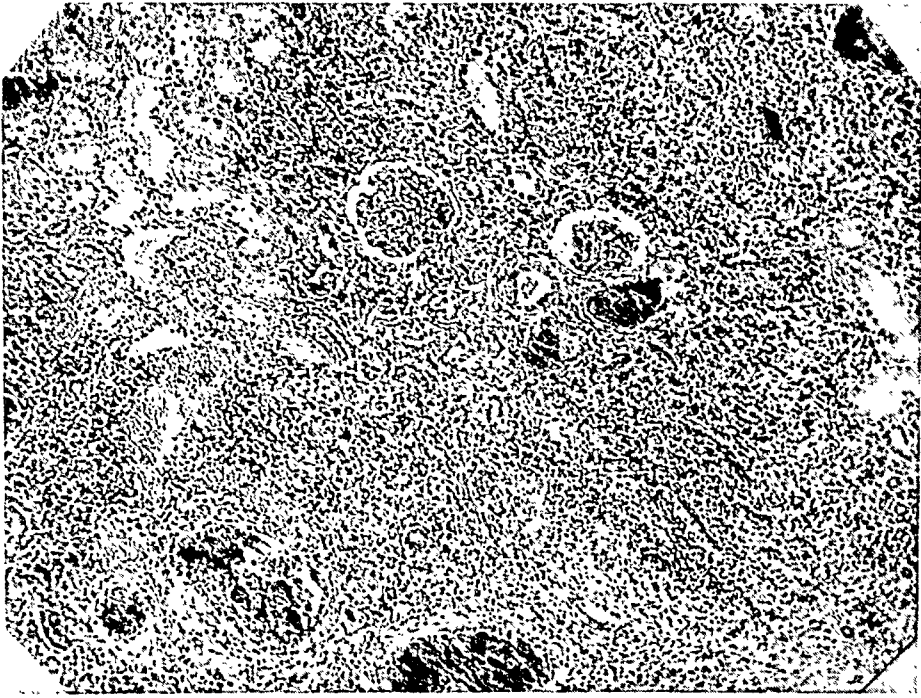


FIG. 6. A section from the kidney in which there is marked nephrocirrhosis with atrophy of the parenchymatous elements. The stroma is increased and there is marked cellular infiltration containing many eosinophiles. There is a secondary change due to arterial involvement. No artery is shown here.

ary anemia, the leukocytosis with an exceptionally high percentage of eosinophiles and the evidence of kidney damage as shown by the urine. The patient was a middle-aged male, and the duration of his illness was 11 months. The only thing of significance in the past history was the presence of a chronic bronchitis or asthma.

A review of the literature on periarteritis nodosa revealed numerous cases of the disease whose symptomatology and physical findings happened to correspond in so many ways with those of our patient that we felt justified in making this diagnosis clinically after biopsy report was obtained.

As can be seen by the postmortem findings in this case, practically all of the smaller arteries were involved. It is surprising that the symptomatology was so slight with so great an arterial involvement. It is true that a summary of many cases reveals a multiplicity of varying symptoms and physical findings, but the majority of these correspond in their most pronounced clinical aspects with the case reported here.

Table 2, which has been compiled by recording many of the symptoms, laboratory findings, and termination of the cases reported by Strong² and since his paper, shows that periarteritis nodosa is a more common disease in males. The age incidence varies from 12 to 71 years. The average age of all cases shown in this table is 36 years.

The onset and duration of the disease shows wide limits of variation. The frequency of rapid and insidious onset is about equal. The duration may vary from six days to two years, as recorded by Strong.² However,

Carr³ reported a patient who lived for six years after the onset of his illness, while both Arkin,⁴ and Troutman⁵ have reported cases lasting four years. Nevertheless, the series reviewed here shows an average duration of 16 months, which is rather higher than it should be as the three very long cases just cited were counted in the computation. Strong's² average was five months, and that of Gruber,⁶ in 57 cases, was four and seven-tenths months.

Three cases reported in English have had serologic tests positive for syphilis. These were studied by Klotz,⁷ Carling and Hicks,⁸ and Gray.⁹

Schottstaedt¹⁰ and Carling and Hicks⁸ each reported a case in which the diagnosis was made before death. An arrest and apparent cure of the disease was accomplished by the administration of salvarsan. In our case the diagnosis was made before death, and treatment with salvarsan given; but no benefit was obtained. Although the immediate cause of death was bronchopneumonia, the autopsy showed that irreparable damage had already taken place in the heart, kidneys, and small arteries.

Loss of weight is uncommonly found, but edema is frequent and was present in our case. It is not certain on what basis the edema is produced. Frequently the damage to the heart and kidneys leads to failure. In our case there was not a noticeable degree of cardiac or renal insufficiency clinically, and we were inclined to explain the edema on the basis of the secondary changes in the tissues produced by the arterial disease. The patient had attacks of paroxysmal dyspnea which may have been cardiac in origin, but cardiac enlargement or failure did not occur.

Fever is frequently observed, and usually is of a low grade hectic type. In some cases of short duration and severe symptoms, temperatures as high as 104° have been reported. This case was afebrile on all but one or two days with the exception of his last few days of life following the onset of bronchopneumonia. Tachycardia was constantly present.

Muscular atrophy, in most cases, is not a prominent physical finding, but in some instances it is very striking. The muscular atrophy and its accompanying extreme weakness were the most outstanding physical signs in this case. This, again, was undoubtedly due to a secondary change, resulting from vascular disease and the marked interstitial myositis. Almost all cases reported have complained of weakness.

Pain in the extremities has been a prominent symptom in a large number of cases. We have classified here all pain in the arms and the legs as neuritis, although in many instances the reports did not state definitely whether or not a true neuritis was present. We were of the opinion that the pain in our case was due to pathologic changes closely simulating neuritis, even though the classical signs of this condition were not elicited. As can be seen from the pathological report, the pain could be explained on the basis of the marked edema of the nerves (figure 4), or possibly by changes found in the muscles (figures 1a and 1c), although neither an active neuritis nor myositis was found.

Abdominal pain has been frequently noted, and in most cases has been found to be due to coronary occlusion or mesenteric thrombosis. This was not a marked symptom in this case and was only noticed on one occasion, at which time an ecchymotic area appeared in the right upper quadrant of the abdomen. This area was very tender to superficial pressure. This was not thought to be due to any disturbance of abdominal or thoracic organs, but rather to rupture of one of the small arteries of the skin or subcutaneous tissue.

The blood pressure is frequently increased. However, in many cases it has not been recorded, and it may be surmised that there was no appreciable deviation from normal in those instances. It seems surprising that the number of cases showing hypertension is not greater in a disease which should produce so great a vascular resistance.

The blood picture in general shows some variation. However, moderate secondary anemia and leukocytosis of 10,000 to 30,000, with a high percentage of polymorphonuclear cells, is the usual thing. Eosinophilia has been recorded in some cases. Lewis,¹¹ Lamb,¹² Strong,² and Schottstaedt,¹⁰ have all reported eosinophilia ranging from 30 per cent to 79 per cent. All of these cases, except that reported by Lewis,¹¹ had asthma. In the case reported by us there was an eosinophile count of 77 per cent, and the patient gave a definite history of asthma. We do not think it probable, however, that such a high eosinophilia as that reported by Strong (79 per cent) and ourselves is to be explained on the basis of asthma alone. We feel that other factors, especially the muscle degeneration, played a large part in these high eosinophile counts.

Most cases of periarteritis nodosa show evidence of renal insufficiency, which may be noted early in the course of the disease or may be merely a terminal complication. In this case the urine showed no albumin, but white blood cells and granular casts were constantly present. The renal function tests were normal.

PATHOLOGY

Periarteritis nodosa is an arterial disease involving the medium sized vessels and often extending into their smaller branches. The vascular disturbance gives rise to secondary changes in organs whose blood supply is decreased.

There is usually a periarterial infiltration consisting for the most part of lymphocytes or polymorphonuclear leukocytes, and often containing a large number of eosinophiles. There are, as a rule, fibrous changes in the adventitia; and proliferative changes in the intima leading to occlusion of the arteries involved. Aneurysmal dilatations and nodular formations of the arteries are commonly seen.

The case reported in this article differs from the majority in that the small arteries and the arterioles, rather than the medium sized vessels, bear

the brunt of involvement. There were no definite aneurysmal dilatations such as are usually seen in this disease. The absence of aneurysmal formations may be explained by the fact that in the instances in which there was evidence of interruption of the continuity of the vessel wall the defects had been filled in with young connective tissue without aneurysmal yielding.

ETIOLOGY

The cause of periarteritis is still unknown. Numerous theories have been advanced, but as yet none of them has been proved conclusively.

Harris and Friedrichs¹³ have shown that periarteritis nodosa may be due to an ultravirus in an experiment in which a suspension was made of the nodules from a case of the disease, and inoculated into a rabbit. The rabbit was killed two months later, and a suspension of its organs was made and filtered. The filtrate was injected intravenously into another rabbit in which the vascular changes seen in periarteritis nodosa developed. This work has not yet been confirmed.

Manges and Baehr¹⁴ believe that periarteritis nodosa is related to rheumatic fever. Although in the case reported here there was no history of rheumatic fever, no evidence of mitral stenosis, and a negative blood culture, there was a definite mitral vegetative endocarditis which is suggestive of a rheumatic etiology.

Swift, Derick and Hitchcock¹⁵ have suggested that the reaction in and around the arteries is of an allergic nature, responding to some cause, possibly bacterial or toxic in character.

Though the presence of *Streptococcus hemolyticus* has been suspected in numerous cases, repeated blood cultures on patients suffering from the disease have been negative.

Vascular disease similar to that seen in human periarteritis nodosa has been observed in dogs and horses suffering from parasitic infestations, and has been described by Cameron and Laidlaw.¹⁶ The possibility that the disease in human beings may be caused by parasitic infestations is suggested by this work and by the eosinophilia, but the finding of parasites has never been reported in any case.

Syphilis and mechanical factors have been discarded as etiological agents.

TREATMENT

There is no specific treatment for periarteritis nodosa. In view of the apparent benefit derived from administration of arsphenamine in cases observed by Carling and Hicks,⁸ and Schottstaedt,¹⁰ but not in our case, it seems advisable that this medication be tried whenever the disease can be diagnosed before death. Symptomatic treatment may be of aid to the patient's comfort.

SUMMARY

1. A case of periarteritis nodosa having some atypical manifestations, both clinically and pathologically, is here presented, occurring in a male, 47 years of age. The duration of the disease was protracted and the course comparatively afebrile. The outstanding signs and symptoms were: generalized progressive muscular atrophy, weakness, pain and edema of the hands and feet. There was no clinical evidence of nodular swellings or aneurysmal dilatations, and the disease was confined to the smaller arteries and arterioles. The immediate cause of death was a terminal bronchopneumonia.

2. The diagnosis was made before death by biopsy.

3. Two cases of apparent recovery by treatment with arsphenamine have been reported in the literature. Six injections of neoarsphenamine were administered to this patient without any evident improvement.

4. An eosinophilia of 77 per cent was noted as an uncommon finding.

5. This case may support the theory of a rheumatic etiology, because of the vegetative endocarditis on the mitral valve margins, or the vegetations may have been a Libman Sacks type of verrucous endocarditis.

REFERENCES

1. HARBITZ, F.: Periarteritis nodosa, Bull. New York Acad. Med., 1927, iii, 17.
2. STRONG, G. F.: Periarteritis nodosa, with report of case, Canad. Med. Assoc. Jr., 1928, xix, 534-546.
3. CARR, J. G.: Periarteritis nodosa, Med. Clin. N. America, 1930, xiii, 1121-1133.
4. ARKIN, A.: Clinical and pathological study of periarteritis nodosa; report of 5 cases, one histologically healed, Am. Jr. Path., 1930, vi, 401-426.
5. TROUTMAN, W. B.: Case of periarteritis nodosa with autopsy findings, Kentucky Med. Jr., 1931, xxix, 144-145.
6. GRUBER, G. B.: Kasuistik und Kritik der Periarteritis nodosa, Zentralbl. f. Herz-u. Gefäßkrankh., 1926, xviii, 145-158; 165-178; 185-198; 205-213; 245-255; 269-277.
7. KLOTZ, O.: Periarteritis nodosa, Jr. Med. Research, 1917, xxxvii, 1.
8. CARLING, E. R., and HICKS, J. A. B.: Periarteritis nodosa, accidentally recognized during life, Lancet, 1923, i, 1001-1003.
9. GRAY, J.: Case of periarteritis nodosa in syphilitic subject, Jr. Path. and Bact., 1932, xxxv, 467-468.
10. SCHOTTSTAEDT, W. E. R.: Periarteritis nodosa with remission of symptoms; report of case, Calif. and West. Med., 1932, xxxvi, 186-188.
11. LEWIS, A. R.: Report of a case of periarteritis nodosa, Proc. Path. Soc. Phila., 1912, N.S. xiv, 134.
12. LAMB, A. R.: Periarteritis nodosa; a clinical and pathological review of the disease, with report of two cases, Arch. Int. Med., 1914, xiv, 481-516.
13. HARRIS, W. H., and FRIEDRICH, A. V.: Experimental production of periarteritis nodosa, Jr. Exper. Med., 1922, xxxvi, 219-230.
14. MANGES, M., and BAEHR, G.: Periarteritis nodosa, Am. Jr. Med. Sci., 1921, clxii, 162.
15. SWIFT, H. F., DERICK, C. L., and HITCHCOCK, C. H.: Bacterial allergy (hyperergy) to non-hemolytic streptococci in its relation to rheumatic fever, Jr. Am. Med. Assoc., 1928, xc, 906-908.
16. CAMERON, H. C., and LAIDLAW, P. P.: A case of periarteritis nodosa, Guy's Hosp. Rep., 1918, lxi, 159-171.

CLINICAL ASPECTS OF PERICARDIAL METASTASIS *

By BEN R. HENINGER, M.D., F.A.C.P., *New Orleans, Louisiana*

METASTATIC lesions of the heart and pericardium have never attracted much attention from a clinical point of view. A thorough review of the literature reveals that only five cases of secondary tumors in the heart and pericardium have been diagnosed ante mortem. In one of the four cases which we are reporting in this paper the diagnosis was made during the life of the patient.

CASE I

A white man, 42 years of age, was admitted to Charity Hospital complaining of pain and swelling of the left side of the chest. The initial symptoms were pain in the left shoulder and a dry cough. Six weeks later the patient noticed a distinct enlargement of the left side of the chest and suffered from dyspnea. He had lost 10 pounds in weight. Apparently no fever was present during this illness and there were no symptoms referable to other systems. The patient was employed as a watchman and his manner of living was not unusual.

Physical examination revealed marked lagging and bulging of the left side of the chest. All the classical signs of a massive left pleural effusion were demonstrated. The heart was displaced to the right. The first mitral sound was greatly intensified and a pericardial friction rub, which was accentuated on expiration, was heard accompanying the diastole. The lower border of the liver was palpable below the costal margin. Results of urinalysis and a blood Wassermann test were negative. An electrocardiogram showed an auricular and ventricular rate of 116. PR and QRS were 0.12 and 0.07 sec., respectively. Inversion of T-waves in all leads was present.

On the day following admission, 1000 c.c. of serosanguinous fluid were removed from the left pleural cavity and were replaced by a similar quantity of air. On two successive days, 650 c.c. and 2650 c.c. of fluid, having identical macroscopic characteristics, were aspirated. A microscopic study of this fluid failed to reveal any evidence of tumor cells. Despite all measures, the patient continued to show severe dyspnea, tachycardia and profound lethargy. The heart rate showed paroxysmal alterations. Four days after admission a right hemiplegia was observed and symptoms of psychosis appeared. Two days later the patient expired, showing manifestations of acute cardiac collapse.

At autopsy,† which was performed by Dr. Emmerich von Haam, 3000 c.c. of cloudy hemorrhagic fluid were found in the left pleural cavity. The right pleural cavity contained a few hundred cubic centimeters of slightly hemorrhagic fluid. The left pleura was greatly thickened and contained numerous nodules of varying sizes which covered the visceral and parietal pleurae. The diaphragmatic pleura was also affected. Acute fibrinous vegetations were visible between the white nodules, which were firm in consistency, and the cut surface revealed white, structureless tissue. A few of these nodules were observed also in the right pleural cavity.

The pericardial sac was extensively displaced to the right on account of the fluid in the left pleural cavity which was partly closed by fibrinous adhesions. The epi-

* Received for publication March 7, 1934. From the Department of Medicine, Louisiana State University Medical Center and the Divisions of Medicine, State Charity Hospital and Touro Infirmary, New Orleans, La.

† Findings presented through courtesy of Dr. Rigney D'Aunoy, Director of Laboratories, State Charity Hospital.

cardium showed numerous white nodules which were of the same consistency as those found in the diaphragmatic pleura. The heart was normal in size. On section, the myocardium was found to be thin and brown; the endocardium was free. All valves were intact. The first part of the aorta showed a few atheromatous and sclerotic areas.

Marked atelectasis of the left lung was present, and the cut surface of the lower lobe showed a tumor about the size of a plum which was undergoing cystic degeneration. This tumor appeared to be in direct connection with the tumor nodules of the pleura. The mediastinal glands were firm and greatly enlarged, and formed a tumor mass which filled the posterior mediastinum. The wall of the trachea was infiltrated by the tumorous mass.

The liver contained one small nodule. The kidneys and spleen contained numerous small white tumor nodules. Section of the brain showed a circumscribed, soft area involving the internal capsule of the left hemisphere and parts of the lenticular nucleus.

Anatomical Diagnosis. Endothelioma of the pleura with metastasis to the epicardium, lungs, spleen, liver and kidneys; and acute encephalomalacia.

Microscopic Findings. Section of the heart showed extensive metastasis of primary tumor cells in the epicardial layer. The surface was covered by a network of fibrin containing numerous polymorphonuclear leukocytes and red cells.

Metastatic nodules were seen compressing the alveoli of the lungs. The lymph vessels were dilated and filled with tumor cells.

Section of the tumor of the pleura showed it to be a malignant endothelioma. Some of the cells showed alveoli which contained a mucoid secretion. Other cell nests showed a concentric arrangement which resembled squamous epithelium, but there was no pearl formation. The stroma in some areas was poorly developed, but was quite abundant in other areas. Single cells presented a variety of atypical forms.

CASE II

A white man, 58 years of age, was admitted to the medical service of Touro Infirmary complaining of loss of weight and weakness which had been gradually progressing over a period of six months. For a month and a half prior to admission, the patient had been confined to his bed. A dry cough and night sweats became evident during the latter part of the illness. The patient's appetite had been very poor and there had been some pain in the right upper abdominal quadrant.

Physical examination revealed an extremely emaciated, cachectic individual. The liver could be palpated two fingers' breadth below the costal margin, and a questionable mass was present in the right side of the abdomen. Distinct tenderness was noticeable in the right upper quadrant.

Laboratory Findings. Red blood cells numbered 4,600,000, white blood cells, 93,500, heterophiles, 96 per cent; blood platelets, 300,000. Wassermann reaction, negative. The urine contained 1.5 per cent moist albumin and a few pus and epithelial cells.

Roentgenographic examination of the chest revealed at the left base, apparently extending outward from behind the heart, an area of increased density which appeared to be striated and sharply defined. The total measurement of the heart shadow was 14.5 cm., while one-half of the inside diameter of the chest measured 13 cm.

The patient was observed for a period of a week following admission. During this time the blood pressure was extremely low—64/40 and 70/40. Tachycardia was noticeable and the heart sounds were of poor quality. The temperature was subnormal and the respirations averaged 25 per minute. Irrationality and stupor preceded death by several days. The condition was diagnosed clinically as a malignancy.

but because the patient was moribund during his stay in the hospital, the primary site of the malignancy could not be determined.

Autopsy* was performed by Dr. J. A. Lanford. The body was extremely emaciated, measuring 5 feet, 9 inches in length and weighing only 96 pounds. The liver was enlarged two fingers' breadth below the costal margin. A rather fluctuant mass which seemed to be encapsulated was palpable in the right retroperitoneum.

The left pleural cavity showed fibrous adhesions between the base of the lung and the diaphragm, and between the pericardium and the pleura. The parietal pericardium was closely adherent to the epicardium. Cellular tissue was irregularly deposited over the entire surface of the heart, but was marked on the posterior surface where it was seen to be infiltrating into the myocardium. This tissue was grayish-white in color and of a semi-firm consistency. The tumor mass extended definitely through the pericardium into the left lung, at the base of which an area of cystic degeneration was found containing purulent matter. This abscess was a neoplastic growth measuring 6 cm. in diameter which had become implanted upon the upper portion of the diaphragm. There was some enlargement of the hilar lymph nodes from metastatic tumor tissue.

The right kidney was removed and a tumor growth of semi-fluctuant consistency, measuring 10 cm. in diameter, was found to be firmly attached to the upper pole. Upon section it was found that the growth occupied the region of the right suprarenal gland and had become infiltrated into the kidney structure. The blood vessels were dilated and there appeared to be some infiltration of the tumor growth into them. The adjacent portion of the inferior vena cava was removed and tumor infiltration was found to have extended through the suprarenal vein into the wall of the inferior vena cava. The kidney itself was normal in size.

Anatomical Diagnosis. Hypernephroma of right kidney; metastatic hypernephroma of pericardium, heart, left lung, and inferior vena cava; toxic hepatitis; septicemia.

Microscopic Findings. Hypernephroma with metastases. The heart was invaded by a secondary new growth and showed a neoplastic pericarditis. (Figure 1.)

CASE III

A negro, 50 years of age, was admitted to Charity Hospital on November 5, 1932, complaining of pain in the umbilical region, loss of weight and progressive weakness, extending over a period of two years. The pain was burning in character and was not related to the ingestion of food. In July 1932, nausea and vomiting had developed and the patient had lost 50 pounds in two months. He had had about 30 injections of salvarsan in the past two years. Physical findings were negative, with the exception of marked asthenia. Roentgenographic examination of the gastrointestinal tract revealed a narrowing of the esophagus at the level of the bifurcation of the trachea. The clinical diagnosis was carcinoma of the esophagus. The patient manifested progressive lethargy and weakness and died on December 17, 1932.

Autopsy was performed by Dr. E. von Haam. The pericardial cavity was normal in size and contained 15 c.c. of clear fluid. On section, the pericardium was found to contain several small tumor nodules, one of which was situated in a small branch of the coronary artery. The heart muscle was brown and friable, the endocardium was free, and the valves were intact.

A tumor mass, about 8 cm. in diameter, was found in the esophagus just below the bifurcation of the trachea. The surface mucosa of this tumor was ulcerated and soft. Another large tumor mass was found at the hilus of the liver. On section the outlines of single lymph glands could be made out and infiltration of the tumor

* Reported briefly at the meeting of the Southern Medical Association, Division of Pathology, November 1932.

into the liver tissue and wall of the stomach in the neighborhood of the cardia, was demonstrated.

Anatomical Diagnosis. Carcinoma of the esophagus with metastasis to peribronchial, retroperitoneal and mesenteric lymph glands and adrenal glands; metastasis to spleen, pericardium, spine, and skeletal system.

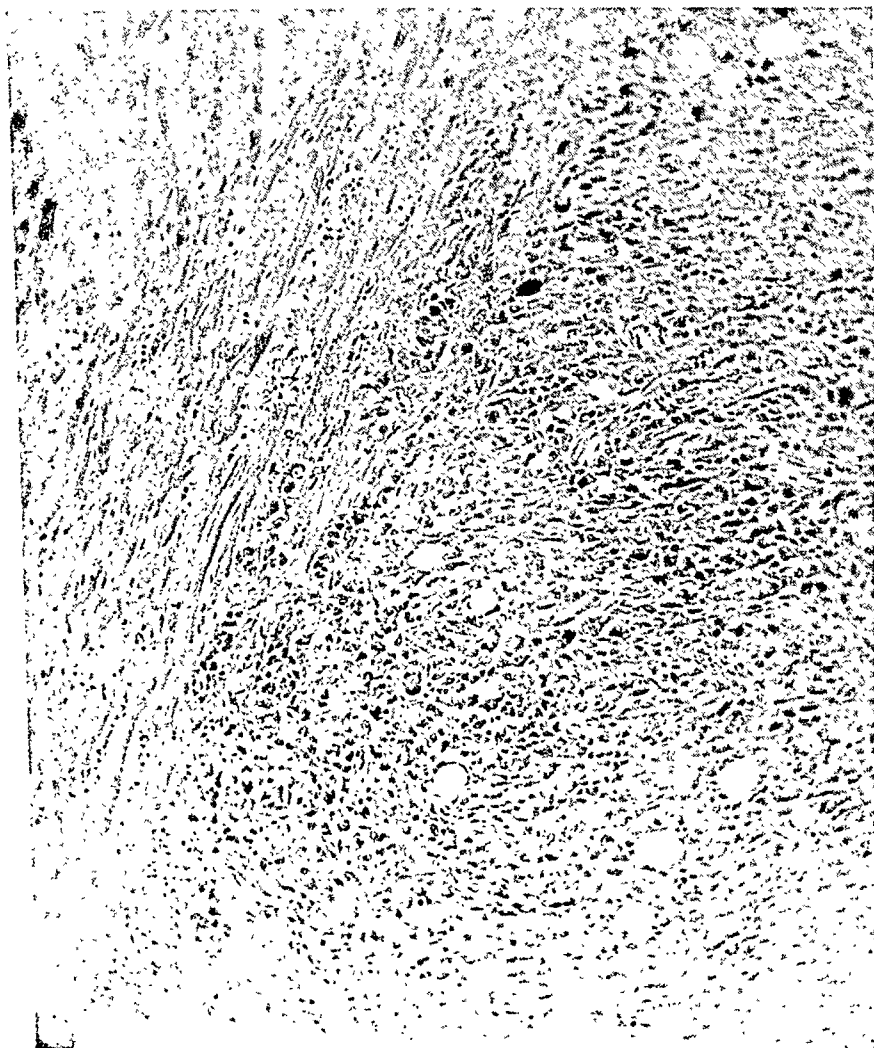


FIG. 1. Photomicrograph of metastasized hypernephroma in epicardium (case 2).

Microscopic Findings. Section of the heart showed tumor metastasis. Section through the retroperitoneal lymph glands showed tumorous tissue which consisted of reticulated cells of a typical character (lymphosarcoma). In some lymph glands, typical carcinomatous metastasis could be distinguished. Section through the esophagus presented the picture of squamous cell carcinoma.

CASE IV

A white man, 51 years of age, was referred by Dr. C. A. M. Dorrenstein, and was admitted to Touro Infirmary on January 28, 1933. The initial symptoms which had appeared nine months previous to that time were chills and fever, dyspnea, cough with prune juice sputum, and progressive loss of weight.

Physical examination showed evidence of considerable loss of weight. An abscess, which was suspected to be of a neoplastic nature, was found at the apex of

the right lung. The patient was very dyspneic. Enlarged nodes were felt in the anterior triangle of the neck, particularly in the left supraclavicular region. Expansion of the right side of the chest was limited. Dullness on percussion over the apex of the right lung extended to the third interspace anteriorly and to the fifth spine posteriorly. Amphoric breathing was heard over the apex of the right lung. The apex impulse was not visible or palpable. On percussion, the left border of the lung was found to extend 15 cm. from the midline. The heart sounds were distant and of poor quality. The rhythm was normal. Definite tenderness was present in both hypochondriac regions, and the liver was palpable three fingers' breadth below the costal margin.

Urinalysis gave negative findings, with the exception of a trace of albumin and a few hyalin casts. Red blood cells numbered 5,115,000 per cu. mm., white cells 17,500, neutrophils, 75 per cent. The sputum was negative for tubercle bacilli, but contained many elastic fibers.

A roentgenogram of the chest made on January 28, 1933, showed that the size of the cardiac shadow had increased tremendously since the previous examination in June 1932. (Figures 2 and 3.) It now measured 8 cm. to the right and 11 cm. to the left or a total of 19.5 cm., while one-half the inside diameter of the chest was 15.25

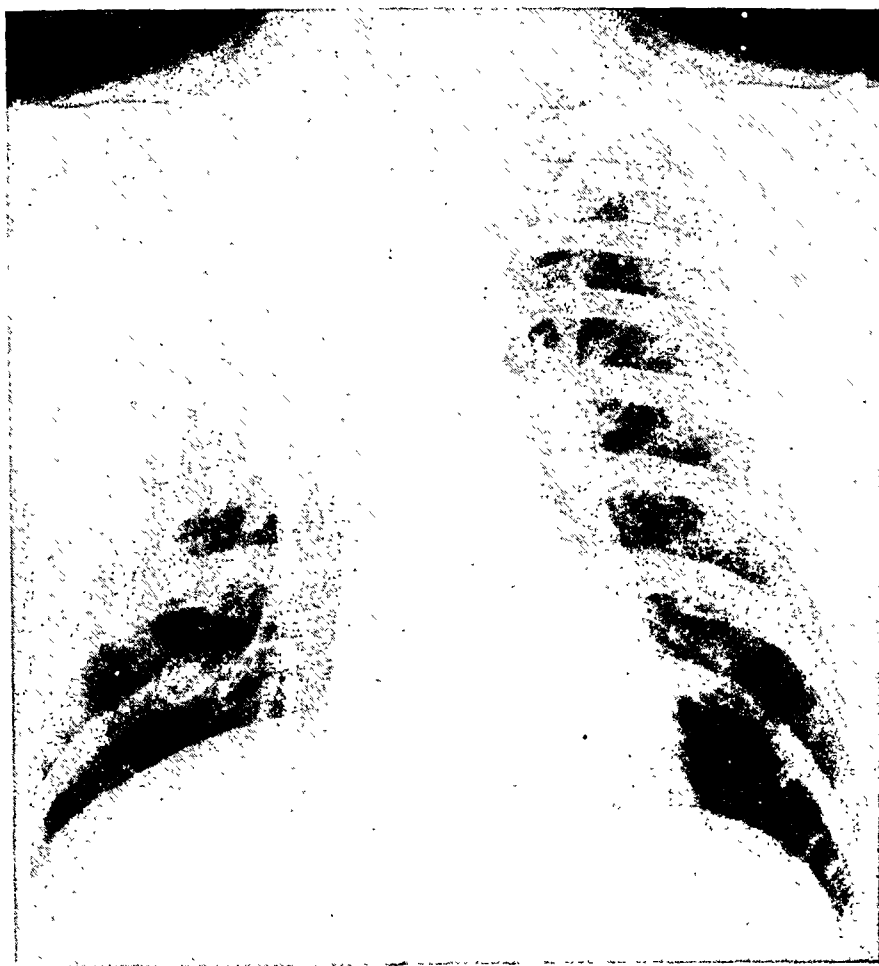


FIG. 2. Roentgenogram of chest before the development of the pericardial effusion. The shadow of the primary carcinoma is seen in the upper lobe of the right lung (case 4).

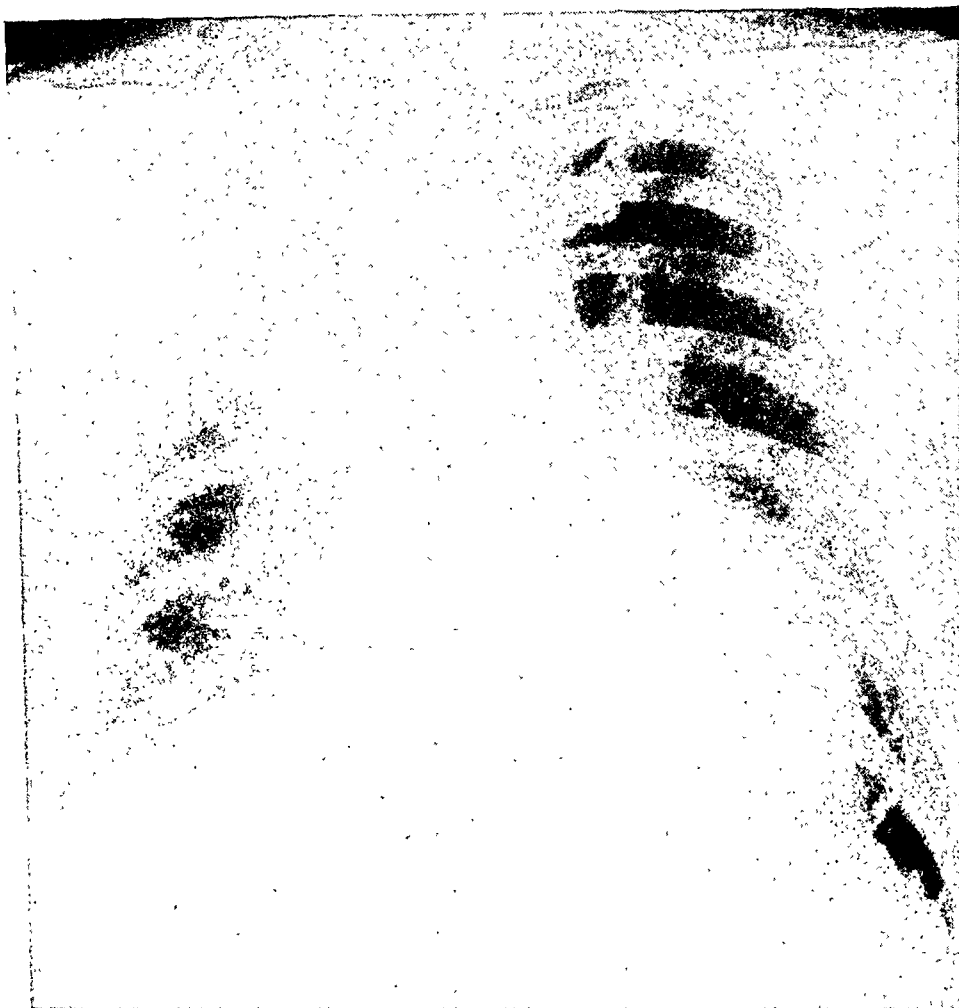


FIG. 3. Roentgenogram of chest after development of the pericardial effusion (case 4).

cm. This indicated an extensive enlargement of the heart, both to the right and to the left, but the width of the aorta had not increased in proportion to the increase in the size of the heart. The lower half of the right lung showed some evidence of congestion, while the upper half was practically obscured by a uniform dense shadow which was considered to be the result of a thickened pleura, with possibly some infiltration of the lung. A slight mottling could be seen through the shadow. The clinical diagnosis was malignancy of the upper lobe of the right lung, with metastasis to the pericardium; and a pericardial effusion.

The patient had no fever during his stay in the hospital. Three days after admission, 4 c.c. of a sanguinous fluid were aspirated from the pericardial sac. This fluid was studied by Dr. J. A. Lanford, who reported the presence of much blood and of undifferentiated neoplastic cells in the sediment. (Figure 4.) The patient grew progressively more dyspneic and died at 9:55 p.m., four days after admission to the hospital.

Autopsy was performed by Dr. J. A. Lanford. Approximately 1000 c.c. of a cloudy, blood-tinged fluid were found in the peritoneal cavity. The liver extended a hand's breadth beneath the costal margin. A small, elevated, white nodule was seen on the anterior surface of the stomach.

The pleural surfaces in the upper portion of the right chest were firmly adherent. Approximately 200 c.c. of sanguinous fluid were found in each pleural cavity. The pericardium occupied almost all of the lower thoracic cavity. Approximately 700 c.c.

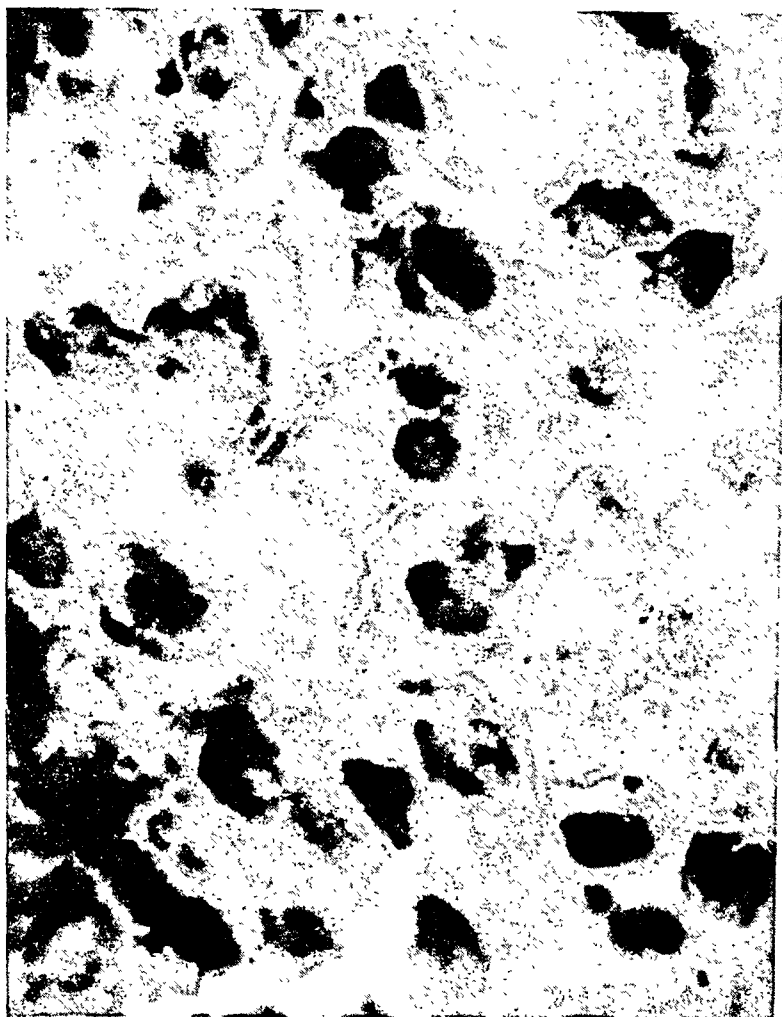


FIG. 4. Photomicrograph of section of sediment from pericardial effusion, showing malignant cells (case 4). (Approximately $\times 2000$.)

of dark, sanguinous fluid were found in the pericardial cavity. The parietal layer of the pericardium was greatly congested and thickened and its surface was granular in appearance. The heart was extremely small and a slight amount of fatty infiltration was seen beneath the epicardium. The myocardium was pale pink in color and was somewhat flabby in tone. The valves were intact. The right lung measured 21 cm. in length and 11 cm. in width. The lower portion was doughy to the touch; the upper portion was very firm and the upper lobe had an almost stony feeling. On section the upper lobe presented a large, circumscribed, sharply defined mass of a grayish-white color. The central portion of this tumor mass showed necrosis and liquefaction.

Anatomical Diagnosis: Primary carcinoma of the lung with metastasis to bronchial lymph nodes, tracheobronchial lymph nodes, mediastinal nodes of left lung, cervical lymphatic chain and the anterior surface of the stomach.

Microscopic examination revealed the presence of primary gland cell carcinoma of the right lung, bronchial in type, showing some inclination to be metaplastic. The pericardium contained neoplastic cells and was greatly thickened as a result of a reparative reaction. (Figure 5.)

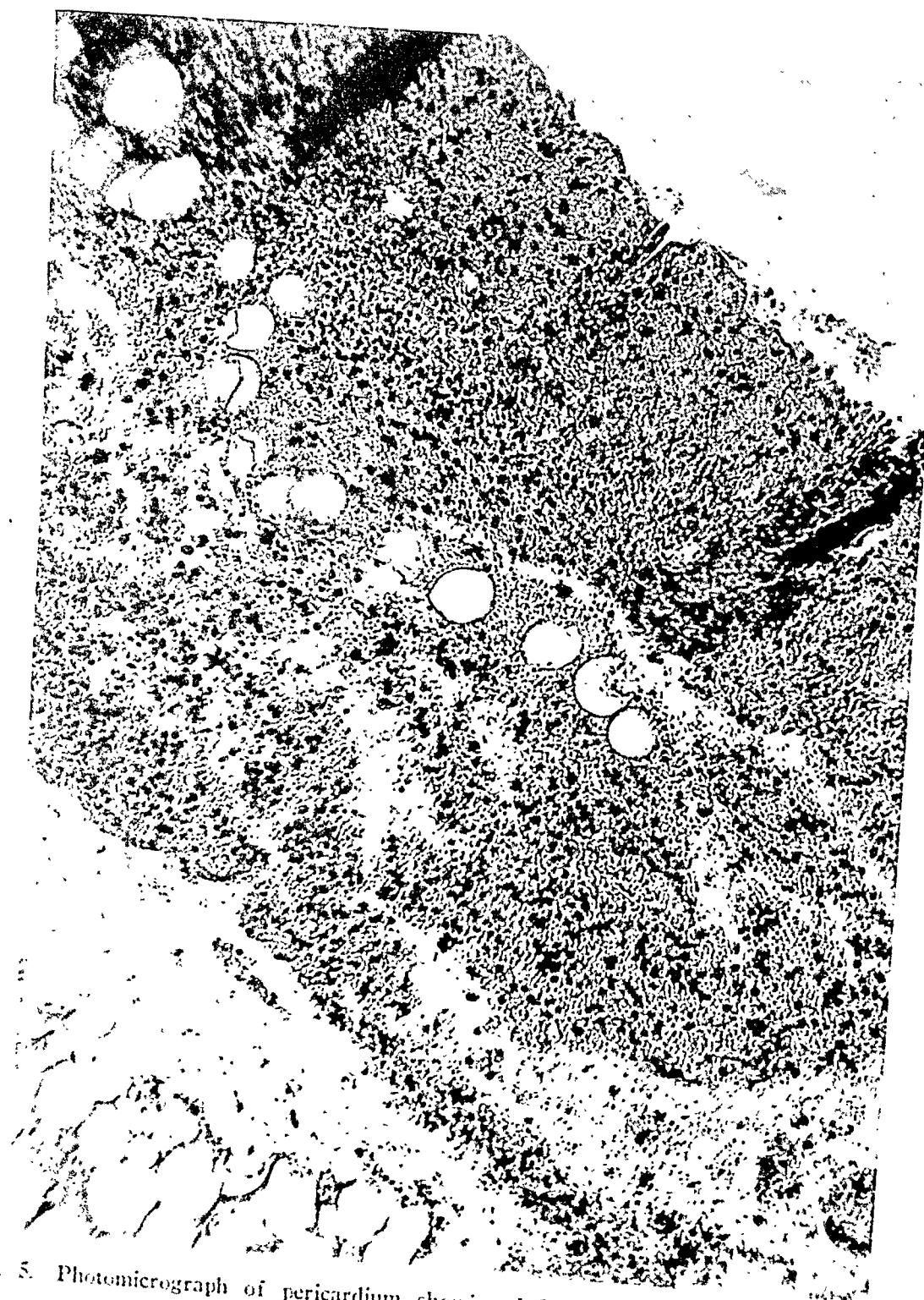


FIG. 5. Photomicrograph of pericardium showing inflammatory reaction and nests of malignant cells (case 4).

DISCUSSION

The scant clinical consideration which secondary tumors of the heart and pericardium have received is by no means justified. Karrenstein¹ reports the finding of cardiac metastases with disseminated growths in 7.5 per cent of a large series of autopsies. It would seem, therefore, that cardiac metastases do occur with a frequency which should merit more attention than they have hitherto received. If the possibility of the existence of such tumors be kept in mind, it seems likely that in many of these cases the diagnosis will be made ante mortem. A consideration of this question may best be preceded by a brief review of pertinent anatomic and physiologic factors.

The pericardium is a fibroserous sac which lies in close proximity to other mediastinal structures. The inner lining is composed of a layer of mesothelium which is continuous with the epicardium at its junction with the great vessels. The lymphatic supply of the heart and pericardium is exceedingly rich. Thick plexuses of lymphatic capillaries are found under the endothelial lining, while in the heart muscle itself, lymph capillaries are more numerous than blood capillaries.

The chief function of the pericardium is that of lubrication. The protective function is of minor importance. The fact that the pericardial sac is practically indistensible when subjected to a sudden increase in pressure explains the symptomatology of cardiac tamponade. A gradual increase in pressure, such as occurs in neoplastic pericarditis with effusion, produces a different sequence of events, for although the pericardial sac is capable of some distensibility when subjected to a slow increase in pressure over a long period of time, a gradual but great accumulation of fluid may give rise to serious cardiac dysfunction. Filling of the inferior vena cava, and later of the auricles, may be seriously interfered with. This mechanism undoubtedly contributed to the cause of death in two of our cases.

Because of the fact that the pericardium does not play a vital part in body economy, tumors affecting this structure are comparatively silent. It is surprising, however, that metastatic growths which have extensively invaded the myocardium often produce very few symptoms, due, it has been said, to the slow development of these growths, and also to the fact that the valves of the heart are not affected. It would seem, however, that this phenomenon demonstrates the remarkable degree of cardiac reserve which the individual may possess.

The work of Yater² and Meroz³ stands out as the most significant contributions in the study of cardiac metastatic lesions. Yater divides these cases into two groups: (1) Those in which cardiovascular symptoms are not manifested, but only such general symptoms as appear in the terminal stages of the disease. Such cases do not lend themselves to diagnosis with the means at our command at the present time.

In cases 2 and 3 of this series, the findings were in no way suggestive of cardiac metastasis. These two cases should be placed in the category of asymptomatic cardiac metastases.

Group 2, those cases in which the symptoms justify the diagnosis of metastatic lesions of the heart or pericardium. Cases 1 and 4 may be placed in Group 2. In case 1 the diagnosis of endothelioma of the pleura should have been made during life, as the signs of pericarditis in association with the pleural effusion were strongly suggestive of a common etiologic factor. Unfortunately the malignant nature of the pleural effusion could not be definitely established before death.

If arrhythmia or signs of cardiac failure develop in a patient in whom a primary malignancy is known to exist, the presence of metastatic lesions should be suspected. In the five cases reported by Fishberg,⁴ Rösler,⁵ and Willius and Amberg,⁶ the diagnosis was deduced in this manner.

In Yater's Group 2, in which symptoms justify the diagnosis and especially so in the event of a pericardial effusion, as depicted in case 4, the author wishes to emphasize the importance of a study of cells from the pericardial fluid as an aid to the diagnosis of malignancy of the heart and pericardium. In a case of this type the fluid should be aspirated and subjected to fixation and sectioning of the sediment.

In case 4 of this series the antemortem diagnosis of malignancy of the pericardium was made in this manner, and later was confirmed by tissue examinations. It is amazing to note that a careful search of the American literature reveals only one other instance, in which the diagnosis of malignancy of the pericardium was made ante mortem and later proved by autopsy, this instance being that reported by Zemansky⁸ in a case of spindle-cell sarcoma. The infrequency with which a cytological study is made of the fluid from pericardial effusions, for diagnostic purposes, is all the more startling when one considers the extreme similarity of the peritoneal, pleural and pericardial sacs. For some years, probably as far back as 1926, members of the Medical Division at the Touro Infirmary have, on several occasions, made use of cytological studies of fluids from the peritoneal and pleural cavities, as an antemortem diagnostic procedure in cases of abdominal and thoracic malignancies. Lanford⁷ has found a surprisingly high degree of correlation between the results of the examination of these fluids from malignant effusions of the peritoneal and pleural sacs and the autopsy findings.

Boyd⁹ stresses the importance of cell studies of fluids from all serous sacs, in the diagnosis of malignancy, and further states that the diagnosis will be confirmed in over 50 per cent of the cases in which malignant cells are encountered in these serous fluids, but emphasizes the important technical point of fixation and sectioning the sediment as against the technic of merely studying a smear. Graham¹⁰ reports a slightly higher percentage of confirmed instances. Both Boyd and Graham mention cases from the peritoneal and pleural sacs exclusively. Zemansky⁸ reports the most elab-

borate and extensive work on the subject to date. In his paper he reports the cytological studies of serous fluids in 113 cases, all of which were checked by subsequent tissue examinations. His percentage of accuracy was even higher, namely, 83 per cent in cases of abdominal fluids and 90 per cent in the pleural effusions. In Zemansky's series of 113 cases, the pericardial fluid was studied in four instances. Three failed to reveal any malignant cells, and subsequent tissue examinations sustained the absence of malignancy of the heart or pericardium, while one case showed malignant cells in the pericardial fluid and likewise showed malignancy of the epicardium at death.

Finally, roentgenographic and fluoroscopic examinations are also of diagnostic aid. Aside from the characteristic contour of the pericardial sac in a case of pericardial effusion, a localized irregularity may in certain cases be demonstrated by careful study. Such an irregularity may be suggestive of a malignant condition in the heart or pericardium, though the differentiation from a mediastinal new growth or aneurysm of the heart may be difficult.

SUMMARY

1. Four cases of metastatic malignancy of the pericardium and heart are reported; in one case the diagnosis was made ante mortem.
2. The relative frequency of metastatic malignancies of the pericardium and heart is mentioned.
3. The value and importance of cellular studies of the fluid from pericardial effusions as a diagnostic aid in metastatic malignancies of the pericardium and heart are discussed and emphasized.

BIBLIOGRAPHY

1. KARRENSTEIN: Quoted by Yater.²
2. YATER, W. M.: Tumors of the heart and pericardium; pathology, symptomatology and report of nine cases, *Arch. Int. Med.*, 1931, *xlvi*, 627-666.
3. MEROZ, E.: A clinical study of three cases of primary tumor of the heart, *Internat. Clin.*, 1917, *iv*, 231-256.
4. FISHBERG, A. M.: Auricular fibrillation and flutter in metastatic growths of right auricle, *Am. Jr. Med. Sci.*, 1930, *clxxx*, 629-634.
5. RÖSLER, O. A.: Vier seltene Herzbefunde. Ein Beitrag zur Herzdiagnostik, *Zentralbl. f. Herz- u. Gefässkrankh.*, 1924, *xvi*, 261-265.
6. WILLIUS, F. A., and AMBERG, S.: Two cases of secondary tumor of heart in children, in one of which diagnosis was made during life, *Med. Clin. N. America*, 1930, *xiii*, 1307-1316.
7. LANFORD, J. A.: (Director of Laboratories, Touro Infirmary, New Orleans, La.) Personal communication.
8. ZEMANSKY, A. P., JR.: Examination of fluids for tumor cells; analysis of 113 cases checked against subsequent examination of tissue, *Am. Jr. Med. Sci.*, 1928, *clxxv*, 489-504.
9. BOYD, W.: Textbook of surgical pathology, 1931, W. B. Saunders and Co., Philadelphia.
10. GRAHAM, G. S.: Identification of cancer cells in serous fluid as diagnostic measure, *Jr. Med. Assoc. Alabama*, 1933, *iii*, 13-16.

SITUS INVERSUS VISCERUM TOTALIS IN SIBLINGS *
CASE REPORTS

By EDWARD A. GALL, M.D., and VICTOR F. WOOLF, M.D.,
New York, N. Y.

MANY congenital abnormalities, being perfectly compatible with normal function, and, of themselves, causing no inconveniences are observed quite accidentally. Falling into this category is situs inversus viscerum totalis, or complete transposition of the viscera.

Single instances of this finding in a family are sufficiently common to occasion no special comment. The statistics vary widely, depending upon the source from which the data have been obtained and the methods utilized in discovering the cases. To quote figures on incidence:

Rösler ¹⁸ —Leipziger Path. Univ. Inst.....	3 :	22,402
LeWald ⁹ —(Recruits—physical examination).....	1 :	35,000
(Autopsy).....	1 :	5,000
(X-ray).....	29 :	40,000
de Goff.....	3 :	60,000
Mandelstamm and Reinberg.....	26 :	39,000
Cleveland ³ (Dissecting Room).....	1 :	10,000
Sherk ¹⁹ —(Mayo Clinic).....	10 :	347,000

We have been able to find records of only 19 instances of two or more cases in the same family, and only 15 occurrences in siblings. Of these, there are only 10 in which there has been unequivocal proof of the actual existence of the condition. It is therefore of interest to present another example of this unusual occurrence. Table 1 is a list of previously reported cases.

TABLE I
Previously Reported Cases of Situs Inversus Viscerum Totalis in Siblings

* Author	Year	Sex	Age	Relation	Proof	Remarks
Rogí ¹⁷	1880	F. M.	20 34	Sister Brother	Hearsay Physical ex- amination	Early pulmonary tuberculosis.
Carpenter	1904	M. M. M.	? ? ?	Brother " "	? ? ?	Cited by Lichtman ¹⁰ but cannot be found.
Doolittle ²	1907	M. M.	41 ?	Father Son	Physical ex- amination Hearsay	Dextrocardia with right hydrothorax; sister has twins (M. and F.) whom patient thought had hearts on the right side.
Reid ¹⁵	1909	M. M.	? ?	Brother "	Hearsay "	Epileptic.

* Received for publication February 14, 1934.
From the Pediatrics Service, Sydenham Hospital, N. Y. C.

TABLE I (Continued)

Author	Year	Sex	Age	Relation	Proof	Remarks
Lowenthal ¹²	1909	M. M.	? ?	Brother "	Hearsay "	
Leroux, Labbé and Barret ⁸	1912	M. M.	7½ 13	Brother "	X-ray "	
Reinhardt ¹⁶	1912	M. M.	20 20	Twins "	X-ray "	Discovered during physical examination for military service. One had dyspnea on exertion.
Neuhof ¹³	1913	F. M.	? 26	Sister Brother	Autopsy report X-ray E. K. G.	Died two years previously of pulmonary tuberculosis.
Curschmann ⁴	1919	M. F.	22 17	Brother Sister	X-ray "	
Ochsenius ¹⁴	1920	M. F.	6¾ 13	Brother Sister	X-ray "	
Brimblecombe ² ...	1920	F. M.	12 10	Sister Brother	X-ray "	Discovered during the course of routine school examination.
Fröhlich ⁷	1922	F. M. M.	4 2 1	Sister Brother "	Operation; X-ray " "	Discovered after laparotomy for appendicitis. Quoted by Landgraf. ⁷
Hofmann ⁶	1926	F. M.	19 12	Sister Brother	Operation; X-ray "	Laparotomy for supposed gastric ulcer; gangrenous cholecystitis found.
Liotta ¹¹	1927	M. M. M.	17 ? ?	Brother " "	X-ray ? ?	Also had pulmonary stenosis and interventricular septum defect.
Bianchi ¹	1927	M. F.	21 30	Brother Sister	Autopsy report Physical examination.	

CASE I

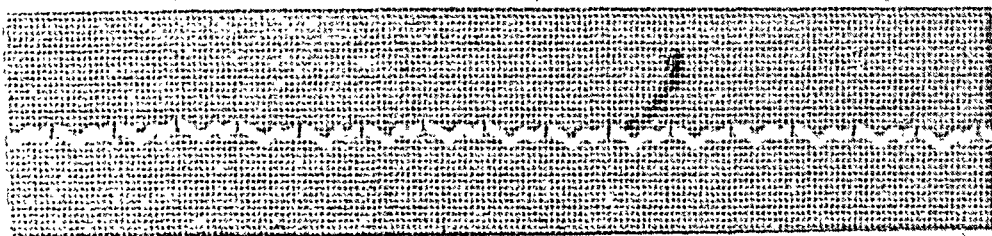
J. J., two-year-old colored female infant, was admitted to the Service of Dr. M. Edelman on December 21, 1930. The child had been ill for six days with a cough of increasing severity and on the day of admission had become febrile and had vomited several times. There was no history of past illness. She had been a full-term delivery, the fourth child in a family of six, all of whom were reported to be alive and well.

Physical examination revealed a well-developed negro child, somnolent, but frequently disturbed by paroxysms of cough characterized by an inspiratory whoop.

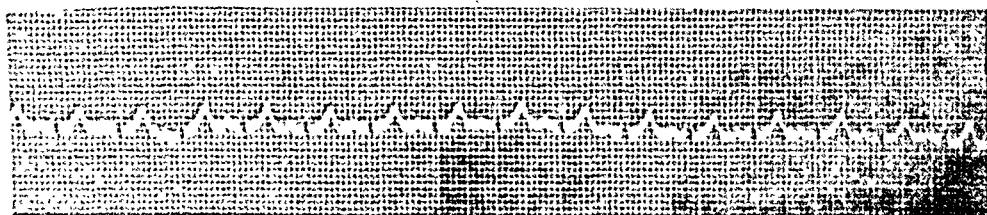
Temperature was 102° F.; pulse 120; respirations 28. The apex of the heart was in the fourth right interspace just within the nipple line. The sounds were of good quality and no murmurs were heard. The second sound in the second right interspace was louder than that on the left. The abdomen was protuberant, but dullness was elicited in the left hypochondrium. The remainder of the abdomen was tympanitic. There were no other gross abnormalities.

A blood count showed a hemoglobin of 62 per cent (Sahli); R. B. C. 4,300,000; W. B. C. 105,000 with polymorphonuclears 24 per cent, lymphocytes 60 per cent, monocytes 6 per cent, and eosinophiles 10 per cent. The electrocardiogram (figure 1) exhibited evidence of dextrocardia and right axis deviation. Roentgenogram of

L I



L II



L III

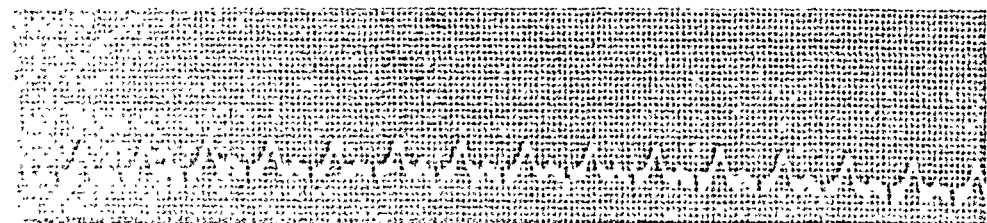


FIG. 1. Patient J. J. Note inversion of all deflections in Lead I and right axis deviation.

the chest and abdomen after a barium meal revealed a complete transposition of the heart and other visible viscera (figure 2).

A diagnosis of pertussis and situs inversus viscerum totalis was made and the child was transferred to the Willard Parker Hospital from which she was eventually discharged as cured of the acute process.

CASE II

O. J., aged four months, sister of the preceding patient, was admitted to the Service of Dr. L. B. Sachs on February 1, 1931. The child had been ill for six days with cough and rhinorrhea. Twenty-four hours before admission she had developed a high fever and considerable respiratory difficulty. The patient had been a full term, normal delivery and had had no significant illness.

The temperature on admission was 104° F. Respirations were labored and were accompanied by an expiratory grunt. There were signs of a diffuse pneumonic process at both bases. The apex beat was palpable in the region of the right nipple. The second sound was most pronounced in the second right interspace. The abdomen was markedly distended and no viscera were palpable or percussable.

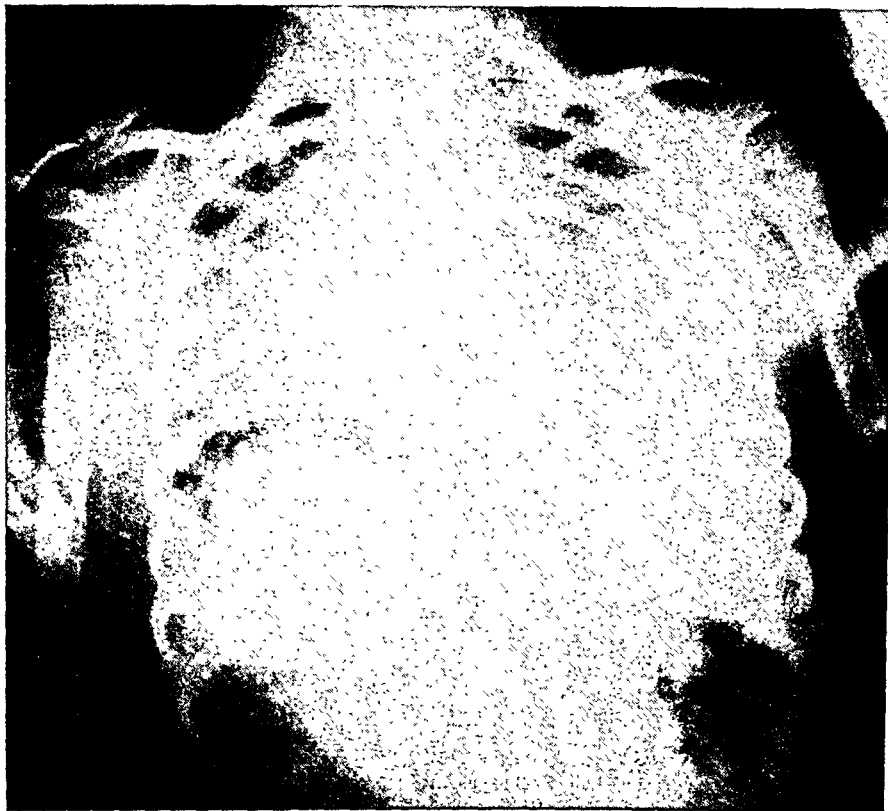


FIG. 2. Patient J. J. Note heart shadow and barium-filled stomach on right and liver shadow on left.

A diagnosis of bronchopneumonia and dextrocardia was made. The patient's condition was critical and, despite supportive measures, she expired three and a half hours after admission.

Postmortem examination showed a complete mirror-image of the normal situs. The heart was situated more to the right than to the left with the apex pointing to the right. The great vessels were transposed as were the abdominal organs. In figure 3 the liver and cecum can be seen on the left and the stomach on the right.

The only other available member of the family was the father. He showed no evidence of visceral inversion, nor did he recall any such occurrence in other members of the family.

SUMMARY

Situs inversus viscerum totalis is reported in two siblings, and 15 previously reported cases are tabulated.

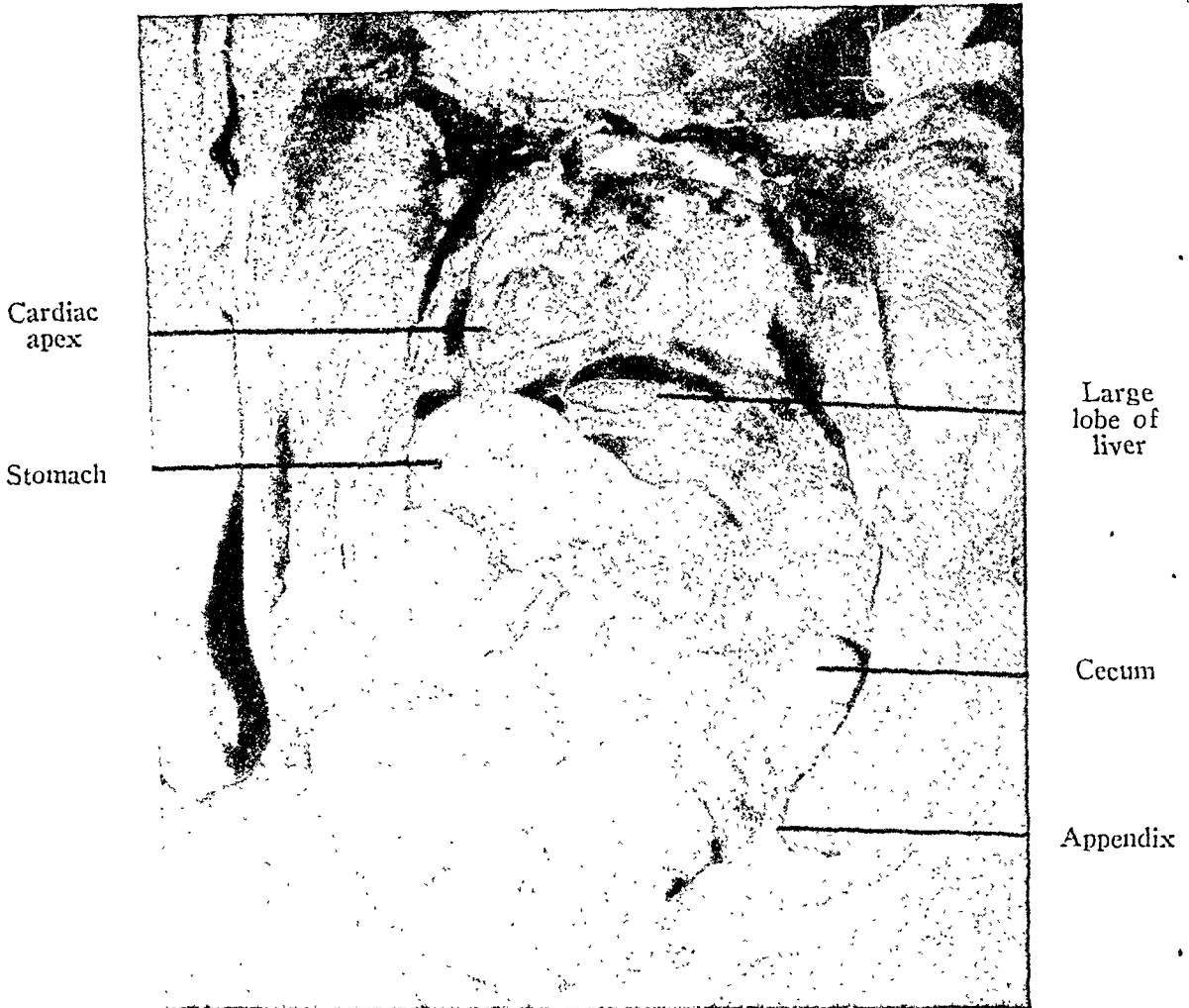


FIG. 3. Patient O. J. Note complete transposition of all viscera in this postmortem specimen.

BIBLIOGRAPHY

1. BLANCHI, S.: Case report, *Riv. med.*, 1927, xxxv, 189. Cited by RÖSLER,¹⁸ also by LICHTMAN¹⁹ in *Pediatrics* 1928, xxxvi, 1221, which in turn refers to *Riv. med.*
2. BRIMBLECOMBE, S. L.: Transposition of viscera in two members of one family, *Brit. Med. Jr.*, 1920, ii, 889.
3. CLEVELAND, M.: Situs inversus viscerum; anatomic study, *Arch. Surg.*, 1926, xiii, 343-368.
4. CURSCHMANN: Familiärer Situs inversus Viscerum totalis, *Anat. Heften*, 1919, Heft 171/73, 405.
5. DOOLITTLE, W. F.: Congenital dextrocardia, *Boston Med. and Surg. Jr.*, 1907, clvii, 662.
6. HOFMANN, A. H.: Familial situs inversus, *Zentralbl. f. Chir.*, 1926, liii, 1633-1634.
7. LANDGRAF: Nachtrag zum Artikel "Appendizitis und Situs inversus," *München. med. Wehnschr.*, 1922, lxxix, 1384. Quoting FRÖHLICH, T.: *Forh. i. Medicinsk Selskab*, 1920, Christiania.
8. LEROUX, C., LABBÉ, R., and BARRET, G.: Inversion viscérale totale chez deux frères de 13 et de 7 ans, *Bull. Soc. de pédiat. de Par.*, 1912, xiv, 297-299.
9. LEWALD, L. T.: Complete transposition of viscera, *Jr. Am. Med. Assoc.*, 1925, lxxxiv, 264-268.
10. LICHTMAN, S. S.: Isolated congenital dextrocardia, *Arch. Int. Med.*, 1931, xlviii, 866.

11. LIOTTA, D.: Situs viscerum inversus complicate a stenosi dell'arteria polmonare e comunicazione interventricolare, *Riforma med.*, 1927, xliii, 869-872.
12. LOWENTHAL, L.: Transposition of the viscera occurring in brothers, *Lancet*, 1909, i, 461.
13. NEUHOF, S.: A case of congenital familial dextrocardia; with electrocardiographic curves, *Jr. Am. Med. Assoc.*, 1913, ix, 1064.
14. OCHSENIUS, K.: Über familiären Situs inversus, *Monatschr. f. Kinderh.*, 1920-21, xix, 27-33.
15. REID, D. M.: Transposition of the viscera occurring in brothers, *Lancet*, 1909, i, 717.
16. REINHARDT: Ein Fall von Situs Viscerum inversus totalis bei Zwillingen (Rekruten), *Deutsch. mil.-ärztl. Ztschr.*, 1912, xli, 931-934.
17. ROGL, E.: Storia di una trasposizione dei visceri, *Sperimentale*, 1880, xlv, 376-378.
18. RÖSLER, H.: Beiträge zur Lehre von den angeborenen Herzfehlern; über die angeborene isolierte Rechtslage des Herzens, *Wien. Arch. f. inn. Med.*, 1930, xix, 505-610. (See p. 511 for list of familial cases.)
19. SHERK, H. H.: Total transposition of viscera, *Surg., Gynec. and Obst.*, 1922, xxxv, 53-57.

REPORT OF A CASE OF DIVERTICULOSIS OF THE SMALL INTESTINE WITH A CRITICAL REVIEW OF RECENT LITERATURE*

By JOHN CHAPMAN, M.A., M.D., *Sweetwater, Texas*

THE literature on diverticulosis of the small intestine prior to 1900 is very scattered and difficult to secure. Since much of it is adequately summarized in later articles, no attempt has been made to extend this present review back farther than 1897.

In that year Grassberger¹³ reported a case of a man 73 years old who was admitted to the hospital in a moribund condition. There was a history of gastrointestinal symptoms of long duration and more recently of hematemesis. Autopsy showed hernial defects of the peritoneum, peptic ulcer, and diverticula of the duodenum, of the first 50 cm. of the jejunum and of the lower 10 cm. of the sigmoid. The jejunal diverticula were numerous, variable in size and shape, situated between the layers of the mesentery. They were of the acquired type called "false," and were empty. Arteriosclerosis was not prominent in heart or kidneys.

Graser¹² two years later reported a case and reviewed some of the previous pertinent literature, devoting especial attention to the work of Klebs and Hansemann which had demonstrated the relation of diverticula to the mesentery and to the larger vessels. Hansemann's work in producing experimental diverticula in the bodies of cadavers was reviewed. Graser injected the inferior mesenteric artery of a female cadaver, fixed the intestine, and found in the colon areas in which the longitudinal muscle was thinned out and in which the circular musculature showed hiatuses. Most of his experimental diverticula evaginated along the mesenteric border at the entry of large vessels through the muscularis. This, it may be remarked, does not coincide with the usual location of diverticula of the large intestine as reported by other authors.^{4, 9, 22} Of special interest in the case reported by Graser was the fact that the patient had suffered severe cardiac symptoms for a number of years and had died in acute failure. The diverticula as in the cadaver experiment were found along the large gaps in the musculature at the points of entry of vessels. These hiatuses had apparently been increased by venous stagnation, since these gaps were relatively slight in bodies in which there had been no circulatory failure. Graser was of the opinion that no great increase in pressure was necessary to produce diverticula since they had been found in cases without a history either of heart failure or of chronic constipation.

In 1900 Fischer¹⁹ reviewed the literature and listed the cases of Moore, Wallman, Birch-Hirschfeld, Klebs, Bristowe, and Hansemann. He notes that at that time all writers except Foerster had agreed that the origin of

* Received for publication February 23, 1934.

diverticula of the small intestine was in relation to mesenteric vessels. In regard to etiology he cites Klebs' view as to the production of a locus resistens minoris in the intestinal musculature by the entry of large vessels. He also mentions Roth's views in regard to fatty degeneration of the muscularis. In his own opinion chronic passive congestion, chronic constipation, traction, and gas pressure were of immediate etiological importance. The first instance he reports is of a pathological specimen 7 cm. long, in which there was a single diverticulum the size of a pea. The mucosal cells were granular and stained poorly, while there was a high degree of inflammation. Fischer also reported an autopsy on a woman 59 years old, in which a great number of diverticula were found in the first meter and a half of small intestine. They were located in contiguity to the vessels, some above and some below the mesentery. In his findings the larger evaginations had small openings, while the smaller ones had large mouths. Microscopically all the diverticula were incomplete or false. They presented an atrophic and granular mucosa with leukocytic infiltration, and the serosa showed a round cell infiltration and increased connective tissue. Microscopically the walls of the blood vessels were thickened.

Ayer¹ reviewed Wallman's case in 1906 and reported an enteric cyst of his own, which, however, does not belong in the category of diverticulosis of the small intestine.

In the same year Gordinier and Sampson¹¹ reported what was probably the first diverticulum recognized at operation. Their patient, a woman aged 45, had suffered from abdominal tenderness and constipation for some time following what was thought to be a severe attack of appendicitis. A large sausage-shaped mass was palpated to the left of the umbilicus, and also another which disappeared after enemata. She suffered constantly from constipation and had passed two enteroliths. At operation the writers found in typical mesenteric relationship 13 diverticula in 40 cm. of intestine. One of these was inflamed and had ruptured. Gordinier and Sampson called theirs the sixteenth reported case of diverticulosis of the small intestine. As to etiology they suggest old age, cachexia, obesity, and chronic passive congestion. Directly inciting is the relation to vessel spaces in the small intestine and to appendices epiploicae in the large. Complications are kinking and rupture. In their opinion there was no safe operative procedure.

In 1918 Braithwaite⁵ reported a case of diverticulosis of the small intestine discovered at autopsy. Each evagination was situated at the mesenteric attachment at a point where a large vessel perforated the muscularis. There were about 60 diverticula in the second, third, and fourth feet of the jejunum, as well as two in the first foot and two in the duodenum. Occurring in coincidence with these were an aortic aneurysm and healing atheromata which led Braithwaite to suggest a possible parasymphilitic etiology for the diverticula.

In reporting two cases discovered by roentgen-ray in 1920, Case⁶ gets credit for being the first to discover diverticula of the small intestine by other

than surgical or postmortem methods. Both of these were in men, one of 61 and the other of 73 years. The diverticula varied from the size of a pea to 5 cm. in diameter, and they were all situated along the mesenteric attachments. In the cases he was able to collect, Case adds to those mentioned above reports from Virchow (multiple jejunal), Buchwald and Janicke (single in a boy of six), Edel (seven diverticula in the jejunum), Seippel (multiple jejunal), Jach (multiple jejunal), Nichols (multiple jejunal), Hodenpyl (multiple), and Boker (multiple in small intestine).

Stetten²⁰ in the next year reported the case of a man 38 years old who suffered severe attacks of abdominal pain without definite localization. There were multiple diverticula of the colon, though there were but two situated about 20 inches apart in the upper ileum. These were grossly injected and inflamed. Resection was followed by cure. These two had been visualized by roentgen-ray and were shown at operation to be mesenteric in placement. However, the small number, the comparatively early age of onset, and the location in the ileum seem to mark this case as not typically that of diverticulosis of the small intestine.

Hunt and Cook¹⁵ also reported two cases, in men of 44 and 54 years. In one there was a history of stomach trouble lasting 15 months and associated with pain and distress in the epigastrium. Eosinophiles numbered 3 per cent. Operation revealed a single true diverticulum, 3 by 3 cm., situated about 3 cm. below the upper end of the jejunum. This was a true diverticulum, though the muscularis was very thin. The mucosa was thickened, and villi, glands, and solitary follicles were present. Attachment was mesenteric. The other case had a history of constipation, vertigo, and diplopia with sharp pains, discomfort, and vomiting. At postmortem, a single diverticulum about 40 cm. below the upper end of the jejunum was discovered. This was located at the mesenteric border and was very thin. As in the previous case of Stetten, these seem not characteristic of the usual disease. Possibly, on account of their situation, relatively early onset, single occurrence, and marked symptomatology, they are more closely akin to the diverticula of the duodenum than to those of the small intestine. However, the question also arises in cases of this kind, in which but one or two diverticula of the jejunum are found, whether or not the writers may have been lucky enough to catch the disease in a very early stage before the characteristic diverticulosis had become widespread.

Another of the somewhat atypical cases was reported in 1921 by MacKechnie,¹⁷ whose patient, a woman of 43, complained of pain, constipation, occasional attacks of vomiting, belching, poor appetite, and prominence of the abdomen. At operation he found the upper end of the jejunum for 2½ feet dilated to a diameter of 2½ inches. Thirteen diverticula, from the size of a split pea to that of a pigeon's egg, were seen. These were thin-walled, collapsible, false, in mesenteric position. The case came to autopsy. Complications given by the writer are ileus, abscess, and perforation.

In the same year McWilliams¹⁹ reported the case of a man of 71 years, who came presenting symptoms of an acute abdominal condition. At autopsy he found the gut distended, bright red with greenish loops, the entire vascularization thrombosed, the lumen full of red fluid, and the large intestine collapsed. On the small intestine were seven large diverticula, one of which was seven centimeters in diameter. In addition he discovered two aneurysms containing clots and established the existence of thrombosis of the superior and inferior mesenteric arteries. This case is also somewhat atypical, and one is more than a little inclined to suspect from the small number of diverticula that they may have been produced by the distention and might not have occurred without the thrombosis. If that is the case, we have something akin to the laboratory distention experiments of early investigators, with evagination occurring along the mesenteric attachment of what was in essence a dead gut.

In 1924 Watson²⁹ reviewed the previous literature, finding previous reports of 29 cases of diverticulosis. His own case was that of a man of 73 who complained of chronic constipation upon which was imposed a syndrome of acute ileus. A firm, round, walnut-sized tumor was palpable to the right of and below the umbilicus. At operation the writer found multiple diverticulosis of the small intestine, one of the largest pouches of which contained an enterolith that had resulted in ileus. The average diameter of the other pouches was one inch, their position mesenteric, in relation to vessels, and their lumens empty. In going over the literature he found the following cases not previously mentioned above: Astley Cooper (multiple), Cornillon (single mesenteric), Osler (multiple), Good (multiple), Taylor and Larkin (multiple), Balfour (multiple), Latarjet and Mirad (single), Terry and Migler (multiple). Eighteen of these had been discovered or confirmed at autopsy, eight had been discovered at operation and two had been reported from roentgen-ray studies. The youngest cases were aged six and 14 years. Fourteen of the cases were in males. In age distribution the great majority were found to have occurred after 40 years and all but five after 50 years. As to etiology Watson suggests senile changes in the muscularis, loss of fat tissue, and dilatation of vascular sheaths. Seven of the 25 cases gave symptoms, which in three cases were obstructive in character.

In the same year Helvestine was able to collect 27 cases. In considering etiology, he ascribed significance to the following factors: increased intra-abdominal pressure due to rectal or vesical tenesmus; atrophy of the circular layers of muscle; and traction on the mesentery by shortened, sclerosed vessels.

Later in the same year Sheppe²⁴ reported a case of diverticulosis discovered at autopsy in a man aged 75, who died of uremia associated with a prostatic carcinoma. There were 54 distinct diverticula beginning 30 cm. below the pylorus and extending downward for 160 cm. The diameter varied from 0.5 cm. to 7 cm. Some of these were situated at the termina-

tion of mesenteric vessels, others were not. They were both separate and fused. The serosa was considerably thickened and composed of dense fibrous tissue. Other findings were endocardial sclerosis, with valvular changes, edema of the lungs, and hernia.

In 1925 Rothschild²³ operated on a woman 63 years old who had had gastrointestinal symptoms for about 15 years. She showed an eosinophilia of 4 per cent and had occult blood in the stools. There was but a single diverticulum $1\frac{1}{2}$ inches in diameter situated to the right of the ligament of Treitz and behind the stomach. The location of the diverticulum was antimesenteric. Associated were a stenotic peptic ulcer and cholelithiasis which may have been instrumental in producing the symptoms and the occult blood, and perhaps may have been in etiologic relationship to the diverticulum. Here again we seem to be dealing with a case that more closely resembles the diverticula of the duodenum than those of the small gut. According to Rothschild's count this was the thirty-third case reported.

Spriggs and Marxer²⁵ in the same year reported the results of a thousand barium meals in which they had discovered diverticula in seven jejunums and seven ileums. As treatment they advocate a medical regime consisting largely of liquid petrolatum and puréed foods, unless the patient presents acute symptoms.

In 1928 Heidecker¹⁴ reported a case of diverticulosis discovered at operation in a man of 54 years. The patient had previously had venous stagnation with uremia and nephritis. At operation more than 30 diverticula, situated along the mesentery and closely crowded, were discovered in the jejunum and duodenum.

In 1931 Miller²⁰ reported the case of a woman, aged 42, whose complaint was distention, cramping, gas eructations and vomiting. At operation he found a single pouch on the convex side of the gut. Its diameter was $1\frac{1}{2}$ inches and the orifice was 1 cm. across. The mucosa was hyperemic and the pouch contained mucus. On microscopical examination a circumscribed round cell infiltration in the muscle layers was found. This, also, is an atypical case in that apparently it was a true diverticulum, antimesenteric in position, and single.

Tengwall²⁸ in the same year reported the case of a woman of 49 years who came to operation for relief of anemia secondary to bleeding from the bowel. In the jejunum 25 cm. below its origin, he found a great number of diverticula extending through a length of 50 cm. They were situated on both sides of the mesentery and varied in size from that of a pea to that of a small hen egg. They were definitely related to the vessels and, according to his account, were classifiable as true diverticula. Tengwall considers the commonest complaint to be bleeding from the bowel with digestive disturbances and meteorism.

Boling³ related that a man, aged 58, was operated upon for intestinal obstruction. At operation 53 diverticula were found, 0.5 cm. to 7.5 cm. apart, with a diameter of from 4 mm. to 3.5 by 5.0 cm. In this case the pouches

began about 30 cm. below the ligament of Treitz and continued through 150 cm. They were all false and mesenteric in position.

The following year Swanberg²⁷ reported the case of a woman of 55 years who gave an account of intermittent stomach trouble over a number of years. There were intervals of vomiting and fairly constant pain in the epigastrium. In the operation to relieve acute obstruction he found a single diverticulum of the jejunum about 8.5 cm. in diameter, the fourth case of its kind.

Erdmann⁹ in 1932, discussing diverticula and diverticulitis, claims to have encountered "many instances" of these conditions through both small and large intestines. He strongly adheres to the congenital theory of etiology and discounts the idea that pouches may be acquired.

Lynch¹⁷ in the same year stressed the relation between the outgrowth of embryonic diverticula and their pathological occurrence. He believed them all to be congenital, while admitting that pouches are more frequent after 35 years and in the male sex.

Duckett⁸ reported the case of a solitary diverticulum of the small intestine which was attached by a fibrous cord to the mesentery. The small intestine became strangulated by slipping through this loop and obstruction led to the death of the patient, a boy aged 2½ years. This seems to be another case in which the findings are markedly dissimilar from the usual ones.

Boyd,⁴ in reviewing the general condition of diverticulosis, came to the following conclusions. The condition is more common in middle and later life. In the small intestine the pouches tend to occur along the mesenteric border. The frequent absence of symptoms is due to the fact that the chyle is liquid and passes this portion of the gut rapidly. Chief among the factors contributing to the condition are weakness of the wall and pressure from within. Other predisposing factors are congenital defects, debilitating disease, senility, chronic constipation, the entry of the vessels through the intestinal musculature, and, in the colon, the attachment of appendices epiploicae.

Rankin, Bargaen, and Buie²² state their opinion that "diverticula represent either a muscular defect or a protrusion of the mucosa through an attenuated spot in the adjacent underlying coats so that there are only two layers in the wall . . . except in the occasional instance in which a true pouch, with all the normal intestinal coats, develops in adult life and possesses greatly thinned out coats." In their opinion traction is capable of producing true diverticula during life even though the pull may not be any more than that exerted by the mesentery.

Beer² in 1904 made as intelligent and complete a study of the subject as can be found in the literature. Even at this date his work is classic for its clear reasoning and wide grasp of the possibilities. It is with good reason that his paper has been chosen to conclude the review of literature, though this removes it far from its chronological position.

He begins with the usual classification of pouches into true and false, congenital and acquired, but remarks that the parallelism is not complete since in some cases acquired diverticula may be true or composed of all four layers of the gut. He remarks further that they may occur anywhere along the gut in great numbers but show some predilection for the sigmoid where they tend to develop around the longitudinal bands and into the appendices epiploicae.

As to etiology, in his review of 18 cases, he concluded that diverticula occur more frequently in old people who not rarely give a history of chronic constipation. According to Klebs, fat people are more prone to develop these pouches, while Hansemann held that lean people are predisposed. These two writers disagreed on mechanical factors also, Klebs favoring traction and Hansemann favoring pulsion. Although Klebs pointed out the relationship to mesenteric vessels his experiments in distention and rupture of the gut are invalid because he was dealing with dead material. As a matter of fact, according to Beer, the weakest point and therefore the place of rupture is opposite the mesenteric attachment in the living gut. Moreover under distention experiments the submucosa was found to be the last coat to yield. In considering Graser's opinion that chronic passive congestion is a frequent etiological factor, Beer points out that congestion has not always been found in cases of diverticulosis, while many cases of circulatory congestion are seen with no diverticula.

Beer's own contribution to the subject of etiology is the opinion that, since the condition tends to appear more frequently in old people, who presumably must have worked-out intestinal walls, muscular insufficiency is an important contributory factor, while the vessels serve to point the way to the evaginating mucous membrane. His microscopic sections of diverticula of the large intestine show a flattening of the glands and epithelium with considerable infiltration of round cells.

REPORT OF CASE: AUTOPSY

The patient was admitted to Osawatomie State Hospital March 30, 1933. His age at that time was said to be 66 years; previous occupation, millworker.

Physical examination performed by one of the staff showed an old man of about the stated age. The blood pressure was 170 systolic and 105 diastolic. The heart was irregular, but otherwise negative, as was the chest. On neurological examination there were marked impairment of gait, poor coördination, sluggish deep reflexes, absent superficial reflexes, and a positive Babinski on the right.

On the basis of the history of a stroke of apoplexy one year previously, and of attacks of vertigo since; and the presence of severe heart failure, edema of the extremities, and the definite neurologic findings he was classified as a case of cerebral arteriosclerosis with psychosis. The following laboratory data are of interest. Blood Wassermann, negative. White cells, 8,850, with 56 per cent polynuclears, 3 per cent transitionals, and the remainder lymphocytes. Red cells, 4,060,000. Hemoglobin, 86 per cent.

On the receiving ward his only complaint was of chronic constipation, for which he demanded and received large doses of laxatives. In the latter part of April 1933

he was transferred to the writer's service where he made no complaints of any kind. However, for several days after his transfer it was noticed that he vomited after each meal. On watching him at table, we learned that he used large quantities of salt. When this was removed the vomiting ceased and he had no further trouble. It must be understood, however, that his mental state was not one that would allow him to recognize defects in his excretions or to mention them if they occurred.

Nothing further of any importance occurred in his case until the night of June 5, 1933 when in walking about he slipped on a piece of wet flooring and fell, fracturing the femur either in the neck or the upper third, and suffering a contused and incised wound in the left frontal region. For the first day following the injury he seemed to be in about his usual condition, but on the second, he sank into a stupor which deepened rapidly and led to his death on the same day, June 7, 1933. The cause of death was not determined clinically, but the following possibilities were noted: (1) hemorrhage, cerebral, which might have produced the fall; (2) possible damage to the brain from the frontal head injury; (3) fat embolism from the broken bone.

Autopsy was performed by the writer on the following day. General examination showed the body of a well-nourished white man of about 65 years. Arcus senilis was present and well developed. The mouth was edentulous. Across the left frontal bone about an inch above the brow was a contused and lacerated wound about two inches long. The left thigh was considerably swollen, and there were abnormal mobility, crepitation, deformity, shortening of the extremity and eversion of the foot. No herniae were noted post mortem, possibly on account of the recumbent position, though they were said to have been found on physical examination during life.

The body was opened and examined in the usual manner. The heart was slightly enlarged, the apex lying in the fifth interspace about 9.5 cm. from the M.S.L. Both ventricles were well contracted and the wall of the left was considerably thickened. Chicken-fat thrombi were found in all four chambers, but they separated with ease and left a shining endocardium. Some endocardial sclerosis was noted, while the aortic cusps were thickened at the base and gave rise to calcareous spikes which reached almost to the free edges of the leaflets. The proximal part of the aorta was smooth except for a few atheromatous plaques in early fatty stages.

The lungs showed an acute bronchopneumonic process, a few apical adhesions and scars, but no evidence of active tuberculosis. A moderate degree of hypostatic congestion was noted.

The liver was normal in size, shape, and position. On section it cut with slightly decreased resistance and excess of blood escaped. The cut section was slightly more friable than normal and the central veins were enlarged and engorged.

The spleen presented a number of unusual attachments about the upper pole and showed a lobulation extending diagonally between the upper and middle thirds. It was larger than normal and the capsule was slightly thickened. On section it cut with decreased resistance and allowed an excess of blood to escape. The surface was very friable, but there was nevertheless an increase in connective tissue.

The genito-urinary system showed fairly advanced arteriosclerotic changes in both kidneys and slight trabeculation of the posterior wall of the bladder just above the trigone.

On stripping the gut one found a considerable length of the jejunum, probably as much as three or four feet, which showed a great number of diverticula opening outward at the mesenteric attachment. Although the walls were much thinner than the intestinal wall, it was thought from gross examination that all coats of the intestine were represented in the diverticular walls. In size the evaginations varied from hardly discernible ones to some that were as much as 4 cm. in diameter. All communicated freely with the lumen of the gut by apertures of varying diameter and none of the pouches contained feces or concretions. The large intestine also presented a few diverticula, smaller than the others and not so definitely related to the

mesenteric attachment. There was no gross evidence of inflammation in these diverticula and nothing to suggest perforation or ulceration. The peritoneal cavity was entirely free from blood and exudate. In the duodenum no diverticula were found.

On examination of the head post mortem, a considerable extravasation of blood was found in the left temporalis muscle. No bone changes were found beneath, however. The skull cap separated with difficulty and meningeal adhesions were noted particularly in the vertical region. Inspection both in situ and in cut section failed to reveal evidence of recent hemorrhage or distortion of the structure. Both lateral ventricles were considerably and uniformly dilated, particularly at the expense of the basal ganglia and of the temporal lobe. The dilatation with increase of fluid affected as well the foramina of Monro, the third ventricle, and the aqueduct of Sylvius. The circle of Willis showed very advanced sclerosis of both internal carotids which were

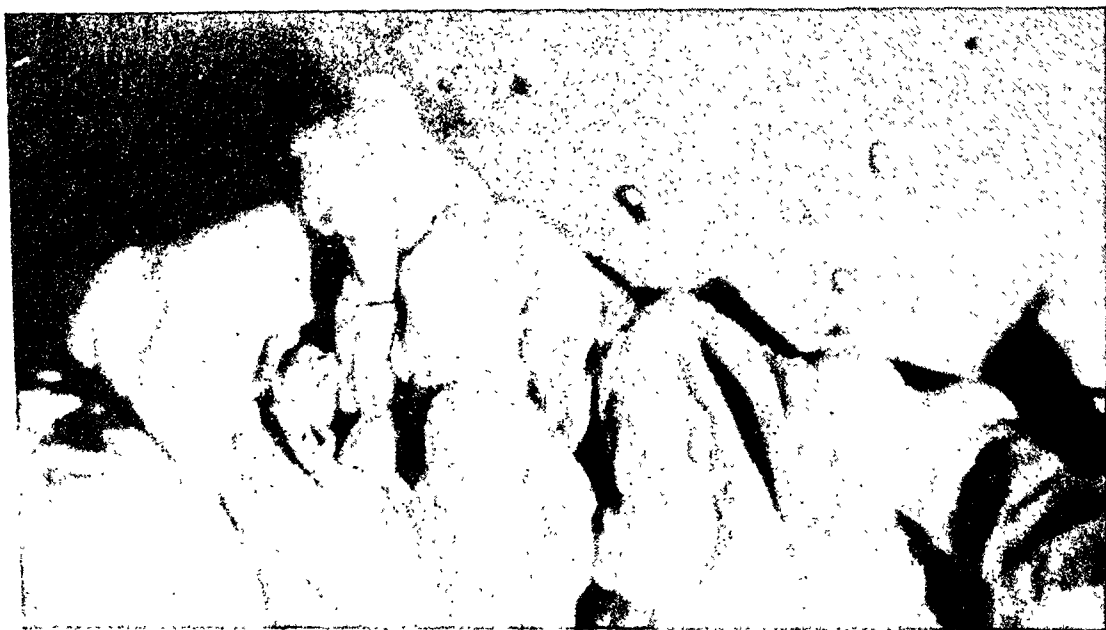


FIG. 1. Diverticulosis of the small intestine.

stiff and brittle. The left vertebral artery was completely occluded and had been replaced by a fibrous cord containing calcium deposits.

Throughout the substance of the brain, involving the basal ganglia and to a less extent the cortex, were empty lacunae varying in size from that of a pea to that of a cherry.

Microscopically, sections of the wall of the diverticula showed but two layers, the mucosa and the serosa, separated by a very thin layer of fibrous tissue representing the submucosa. The fibrous tissue seemed to be partly transformed into hyaline, though there was no calcareous infiltration. In this layer also were situated both veins and arterioles with considerably thickened walls. However, it is rather remarkable that arterioles were exceedingly few, very small, and in one or two cases almost obliterated. The mucosa was eroded, probably post mortem, but cell outlines persisted clearly enough to make apparent a marked atrophy of the mucosa and flattening of its cells. In the tissue beneath was an infiltration chiefly of round cells. A few polymorphonuclear leukocytes were seen, but no eosinophiles. Sections made through the bases of the diverticula showed scattered muscular elements, mostly transverse in direction. These fibers evidenced fragmentation, which might have been artefactual, but which on account of the poor staining and relative paucity of nuclei we were in-

clined to believe at least partly of degenerative origin. Goblet cells were seen frequently in the mucosa of this part of the pouch.

DISCUSSION

Classification. The first division suggested was that of congenital and acquired. Somewhat later, as etiology came to be more fully considered, writers began to speak of diverticula as being "true," that is, composed of all the normal coats, or "false," lacking some of the normal intestinal layers. For a time there was thought to be a complete parallelism between the terms, but Beer objected to this view on the ground that acquired diverticula may in a few cases have all the coats, though in a greatly thinned-out condition. Somewhat later writers began to use the terms "complete" and "incomplete" rather than true and false, claiming that the new terminology was a more exact one. Combinations of these classifications are still in use.

However, before we can undertake to discuss the subject it seems worth while to consider if further subdivision may not be necessary. No little confusion has already arisen in the literature because of improper or imprecise definition, so that it seems necessary to emphasize the fact that it is a mistake to consider all diverticula of the gastrointestinal tract as similar or related merely because they happen to bear the same name and to occur in the same system.

If the discussion is confined to only those pouches involving the small intestine below the duodenum (since the duodenum must be considered separately on account of anatomical differences in its attachment, glandular structure, and pancreatic relationships) it is still not enough to say that diverticula of the small intestine are confined to the congenital type of Meckel and the acquired type of multiple diverticulosis.

With the duodenal type, which differs from the typical picture in number, age at onset, attachment to the gut, and severity of symptoms, should probably be included those cases described by Stetten, Hunt and Cook, MacKechnie, and Miller. In these cases there were either solitary or very few diverticula, mostly of considerable size, some of them complete, not all in definite relation to the mesentery, and most of them giving rise to fulminating symptoms. These, it will be noted, are often spoken of as being at the beginning of the jejunum, while the more characteristic case of multiple diverticulosis is frequently spoken of as taking rise about 30 cm. below the duodenal-jejunal junction.

When solitary, complete, and rather large diverticula of the jejunum are spoken of, moreover, one is a little inclined to think they may perhaps be anomalously located diverticula of Meckel, since Waterston³⁰ writes that he has found that vestigial organ at a distance of as much as 12 feet from the ileo-cecal valve. But the cases excluded need not be considered certainly as being Meckel's pouches, since evaginations in embryonic life are typical of the gut.

For purposes of discussion, therefore, one is perhaps justified in defining multiple diverticulosis of the small intestine as the formation of a great number of pouches, consisting usually of only two intestinal coats, characteristically located in the jejunum and ileum at or near the mesenteric attachment.

Etiology. If the atypical cases are excluded, there belong in the category as it has been defined, so far as I have discovered, 32 cases. The cases of Buchwald and Janicke, Stetten, Hunt and Cook, Cornillon, Latarjet and Mirad, Rothschild, Miller, Swanberg, and Duckett are omitted as not meeting the requirements of the definition. Of the 32 cases concerning which I have found information, 13 occurred in males, 8 in females, a slight preponderance of males which with more adequate data might be nearly equalized, since none of the factors frequently operative in producing diverticula of the bladder is here concerned. If intestinal stasis is of etiological importance, it might even appear that women rather than men should show a preponderance since, as a result of pregnancy and child-bearing, females are likely to be subjected more often to constipation than males.

The average age of the males of whom information was found was 62.8 years, while two were spoken of as "old." The average age of the women is 59.7. In men the range is from 40 to 85 years, in women from 43 to 77 years. Naturally this does not represent the actual age of onset, since 24 of the cases were discovered at autopsy. Nevertheless the impression is left clearly by all writers that in their opinion multiple diverticulosis as here described is a disease of older people.

Since Graser has mentioned the importance of chronic passive congestion in production of diverticula, a study was made of the cases upon which information was available. In only 5 of the 32 was there either history or evidence at autopsy of heart disease, while in only three was there history of frank heart failure. Beer in his paper, moreover, rather effectually disposed of this contention.

Immediate factors to be considered are largely mechanical. They consist primarily of the relation between the pressure within the intestine and the traction of the mesentery on its wall. When one remembers that the majority of cases considered occurred in the jejunum, where gas pressure is relatively slight on account of the paucity of bacteria in this region, while accumulation of feces is impossible on account of the fact that the chyle is in liquid form, and that stasis in this portion is relatively slight, he will perceive that the possibility of diverticulum formation through pressure is rather remote. Beer's experiments which show the rupture point of surviving intestine to be antimesenteric will also be recalled. Still another point worth consideration is that the wall of the jejunum is thicker than that of the ileum, yet most of the cases showed the greatest numbers of pouches in the jejunum. Pressure, moreover, is relatively greater in the ileum than in the jejunum on account of increase in bacterial growth and comparative stasis at the ileo-cecal valve.

If Klebs' idea that pouches develop at the point where vessels perforate the walls of the intestine is considered, it will be remembered that he made this statement to explain the mesenteric position of most diverticula. Yet the mesenteric branches on reaching the gut, instead of penetrating the muscle at once, divide into two branches, superior and inferior, and course over the muscularis just beneath the serosa, sending branches through the muscles at intervals until the antimesenteric point is reached.³⁰ Nor would this explanation account for the antimesenteric position of diverticula of the large gut, in which vascularization is accomplished in a similar manner.

If the traction theory is considered, it will be found likewise unsatisfactory. If traction were of great importance one would be justified in expecting the transverse colon to be the seat of election for diverticula, with the stomach in perhaps second place, since ptosis is common in both of these; yet both these organs are relatively immune. Indeed, aside from the small intestine, the most frequent sites are the sigmoid and the duodenum, both of which are rather firmly held in position. Nor is there reason to think that the tug of the jejunum on its mesentery would be severe enough to produce fifty or more diverticula in the first three or four feet of its length.

Fischer remarked that in his case the blood vessel walls were thickened, and Braithwaite much later noted an aneurysm with healing atheromata in connection with his case. Both of these may have suggested to Helvestine the possibility that it was perhaps sclerosed and shortened vessels which produced the requisite traction. But there is no great reason to think that sclerosis would be restricted to the jejunal branches of the superior mesenteric artery, and if it is not, the same difficulty is found as in the original traction theory. But, as will be pointed out later, there is a possibility that sclerosis may occur in a rather specific manner at this point. If this is true, Helvestine's suggestion is of value.

Beer seems to have been the first to suggest the rather obvious possibility that degeneration of the musculature of the intestinal wall may be of etiological importance. Braithwaite, too, apparently had some such idea when he suggested a possible parasymphilitic origin of diverticulosis, though he did not explicitly state that degeneration of muscle might occur. Helvestine, also, considered atrophy of the muscular layer as one important factor in etiology. Boyd speaks only of weakening of the wall, combined with pressure from within. Our own sections seem to bear out the possibility of such a situation. Nevertheless it does not seem reasonable to suppose that atrophy or degeneration should be more prominent in the jejunum than elsewhere, unless there is some predilection of the superior mesenteric artery to early sclerosis, for the jejunum is certainly less subject to distention than other portions of the bowel. Moreover, as its name suggests, in its characteristic condition it is empty.

All of these considerations, however, omit one fairly simple and obvious fact. Beer alone made the note in his discussion that in his distention experiments the submucosa was the last coat to yield before rupture. Yet

not only all his successors, but even he himself overlooked the importance of his statement.

Lord Moynihan²¹ writes of the submucosal coat: "The layer which it is of the chiefest importance to secure, in order that the suture may hold well, is the submucous coat. This, as shewn by S. D. Gross and Halsted, is of great strength and toughness. . . ." And Waterston³⁰ states, "The submucous coat is a loose but strong layer of areolar tissue, . . . on which chiefly depends the strength of the intestinal wall."

It would seem then that to approach the subject of diverticulosis satisfactorily, one must find something to account for weakening of the submucosal layer. The most exact analogous condition thought of is the arteriosclerotic aneurysm. In both aneurysms and diverticula, a hollow tube is subjected to varying degrees of pressure. In both, lining layers (mucosa and endothelium followed by submucosa and subendothelial connective tissue) are surrounded by layers of muscle and elastic tissue. In aneurysms the process begins either in the media or in the intima from which it extends to the media, the result in any case being a weakening of the elastic structure, while the systoles produce a hammer-like pounding within. In the intestine, I am attempting to explain diverticula on something of the same basis: changes in connective tissue, loss of elastic tissue, something analogous to hyaline changes in the submucosa, and finally hammer-like changes in pressure due to rapid contractions alternating with periods of complete emptiness. If this assumption is correct, there would seem to be good reason for Braithwaite's guess at the parasymphilitic origin of some intestinal diverticula. It also becomes clear why acquired diverticulosis should appear so frequently in old people, whose elastic and connective tissue very characteristically undergo atrophy, even in the skin.

There would remain for explanation, if the hypothesis should be true, why these senile tissue changes should be especially prominent in the jejunum. For this I can offer no suggestion unless it may be that this, which is one of the most active and glandular portions of the gut, undergoes a selective and early degeneration on account of its normally great activity.

Of course there are to be considered as always the possibility of a hernial propensity, which seemed particularly marked in my own case. The objection to such an idea is that a great many men have hernias who do not have diverticula, while but few women have hernias though they appear to be on a nearly even footing with men in diverticulosis. As for the possibility of hereditary or congenital maldevelopment, though it may be plausible, yet these adjectives have served so long to excuse lassitude that consideration of them should be altogether omitted until other resources are exhausted.

Pathology. Fischer was among the first to describe the typical atrophic and flattened mucosa. In his case there were also leukocytic infiltration, increased connective tissue in the serosa combined with round cell infiltration, and thickening of the vascular walls. In Sheppe's case the serosa was considerably thickened and composed of dense fibrous tissue. Miller's

somewhat atypical case showed round cell infiltration in the muscular layers. Beer describes similar lesions and the findings in the present case also coincide with this description.

Symptomatology. Omitting the questionable cases before alluded to, there have been nine of the 32 cases which presented symptoms. In five of these, symptoms were relatively inconspicuous, while in the remainder acute ileus supervened. Grassberger's case is not included in these, since the symptoms apparently related chiefly to the coincident peptic ulcer. In McWilliams' case the symptoms were definitely those of a mesenteric thrombosis. The remaining three cases which came to operation presented the symptoms that might be expected to follow from perforation, obstruction, ileus, or abscess. In my own case as in many there was nothing to draw particular attention to the bowel, the symptoms being only chronic constipation, with perhaps mild pain in the abdomen or discomfort.

Diagnosis. Differentiation of multiple diverticulosis of the small intestine is very difficult and must be said to rest upon roentgen-ray studies and the elimination of other possibilities. In some cases there have been palpable sausage-shaped masses situated near the umbilicus, sometimes on the left side. Volvulus, intussusception, and malignancy would need to be ruled out. Blood counts are apparently not of any great help, though two cases are mentioned in which was found an eosinophilia of 3 and 4 per cent. The cases of obstruction could not be diagnosed with exactness, since gall-bladder disease, appendicitis, volvulus, intussusception, mesenteric thrombosis, and the other acute abdominal conditions would have to be considered.

Treatment. In many cases one would probably never be aware until postmortem examination or barium study had been made that he was treating diverticulosis. In those definitely diagnosed without operation, the method of choice is probably the medical treatment suggested by Spriggs and Marxer: bland diet of low residue and mineral oil lubrication. To this might be added an occasional course of bismuth, though it would probably be of little use in preventing the development of severe obstructive complications. In those patients who present themselves with acute abdominal symptoms, the treatment is obviously laparotomy with resection and end-to-end anastomosis.

SUMMARY

1. The literature in regard to intestinal diverticulosis is reviewed.
2. A new case of multiple diverticula of the jejunum is presented.
3. A change in classification is suggested.
4. The etiology of the condition is reviewed and the importance of submucosal failure as the chief element in the production of pouches is stressed.

BIBLIOGRAPHY

1. AYER, J. C.: Enteric and mesenteric cysts, with report of an unusual case, *Am. Jr. Med. Sci.*, 1906, cxxx, 89-108.

2. BEER, E.: Some pathological and clinical aspects of acquired (false) diverticula of the intestines, *Am. Jr. Med. Sci.*, 1904, cxxviii, 135-145.
3. BOLING, J. R.: Multiple diverticula of jejunum with resection, *Jr. Am. Med. Assoc.*, 1931, xcvi, 526-527.
4. BOYD, W.: *Surgical pathology*, 1925, W. B. Saunders Co., Philadelphia, p. 307.
5. BRAITHWAITE, V.: A case of diverticulitis of the small intestine, *Guy's Hosp. Gaz.*, 1918, xxxii, 77.
6. CASE, J. T.: Diverticula of small intestine, other than Meckel's diverticulum, *Jr. Am. Med. Assoc.*, 1920, lxxv, 1463.
7. DAVID, V. C.: Diverticulosis and diverticulitis, with particular reference to development of diverticula of colon, *Surg., Gynec. and Obst.*, 1933, lvi, 375-381.
8. DUCKETT, J. W.: Diverticula of small intestine, *Texas State Jr. Med.*, 1932, xxviii, 473-475.
9. ERDMANN, J. F.: Diverticulitis and diverticulosis, *Jr. Am. Med. Assoc.*, 1932, xcix, 1125-1128.
10. FISCHER, M. H.: False diverticula of the intestine, *Jr. Exper. Med.*, 1901, v, 333-352.
11. GORDINIER, H. C., and SAMPSON, J. A.: Diverticulitis (not Meckel's) causing intestinal obstruction, multiple mesenteric (acquired) diverticula of the small intestine, *Jr. Am. Med. Assoc.*, 1906, xlii, 1585-1590.
12. GRASER, E.: Das falsche Darmdivertikel, *Arch. f. klin. Chir.*, 1899, lix, 638-647.
13. GRASSBERGER, R.: Ein Fall von multipler Divertikelbildung Darmtractes, complicirt mit peptischem Geschwür am Pylorus, *Wien. klin. Wchnschr.*, 1897, x, 149-151.
14. HEIDECKER, H.: Multiple Divertikelbildung des Duodenums und Jejunums, *Beitr. z. klin. Chir.*, 1928, cxlii, 776-783.
15. HUNT, E. L., and COOK, P. H.: Jejunal diverticula, *Ann. Surg.*, 1921, lxxiv, 746.
16. CAPLAN, A., and TINDALL, W. J.: Two unusual cases of diverticulosis, *Lancet*, 1932, ii, 896-897.
17. LYNCH, J. M.: Diverticula and diverticulitis, *Jr. Am. Med. Assoc.*, 1932, xcvi, 973-977.
18. MACKECHNIE, H. N.: Diverticula of jejunum, *Ann. Surg.*, 1921, lxxiv, 96.
19. MCWILLIAMS, C. A.: Diverticula of the jejunum, *Ann. Surg.*, 1921, lxxiii, 135.
20. MILLER, A. M.: Isolated diverticulum of jejunum, *Am. Jr. Surg.*, 1931, xi, 116-117.
21. MOYNIHAN, B. G. A.: *Abdominal operations*, Vol. I, 1926, W. B. Saunders Co., Philadelphia, p. 467.
22. RANKIN, F. W., BARGEN, J., and BUE, L. A.: The colon, rectum, and anus, 1932, W. B. Saunders Co., Philadelphia, p. 137 et seq.
23. ROTHSCHILD, N. S.: Diverticula of jejunum, *Ann. Surg.*, 1925, lxxxii, 250-255.
24. SHEPPE, W. M.: False diverticula of jejunum, *Jr. Am. Med. Assoc.*, 1924, lxxxii, 1118-1119.
25. SPRIGGS, E. L., and MARXER, O. A.: Intestinal diverticula, *Quart. Jr. Med.*, 1925, xix, 1-34.
26. STETTEN, DEW.: Multiple diverticula of upper ileum, *Ann. Surg.*, 1921, lxxiii, 241-244.
27. SWANBERG, H.: Solitary diverticulum of jejunum; report of case diagnosed roentgenologically, *Radiol. Rev. and Chicago Med. Rec.*, 1932, liv, 197-199.
28. TENGWALL, E.: Case of multiple diverticula in jejunum, *Acta. chir. Scandinav.*, 1931, lxxviii, 162-170.
29. WARREN, C. M.: Diverticula of jejunum; case with enterolith causing intestinal obstruction, *Surg., Gynec. and Obst.*, 1924, xxxviii, 67-71.
30. WATERSTON, D.: in CUNNINGHAM, D. J.: *Textbook of anatomy*, fifth edition, 1927, W. Wood and Co., New York.

ELECTROPYREXIA

A RÉSUMÉ OF THERAPEUTIC APPLICATIONS AND TECHNICS *

By STAFFORD OSBORNE, B.P.E., and D. E. MARKSON, M.D., F.A.C.P.,
Chicago, Illinois

FEVER therapy has received the serious attention of investigators in the field of clinical research, not only in this country but also abroad. The mass of evidence so far presented indicates that fever per se has a definite therapeutic value. Its range of application is such that it merits the consideration of the general practitioner as well as the specialist. Unfortunately, the many articles dealing with this procedure are widely scattered throughout the medical literature. The purpose of this paper, therefore, is to review the therapeutic applications of electrically induced fever as well as briefly to outline the proper technic indicated in these different conditions.

The treatment of arthritis by hyperpyrexia was introduced by Markson and Osborne¹ in 1931. In their subsequent reports^{2, 3} a two years' experience with this therapy is reviewed and the clinical results tabulated. Other authors^{4, 5, 6, 7} have since endorsed this type of therapy in arthritis. Of course, the results depend to a great extent on the type of case selected for treatment and this is probably worthy of reëmphasis here. The hypertrophic, or degenerative, type is now excluded entirely because of the high incidence of associated cardiorenal damage in these patients. They do not tolerate electropyrexia well and are subject to such accidents as myocardial failure and fibrillation. Cases are now selected from the infectious group only as this younger group withstands the high fever without serious danger or discomfort. Infectious is here used synonymously with rheumatoid of the British, and proliferative, described by Nichols and Richardson.⁸

There are differences of opinion among the various workers regarding the height and the duration of the fever curve that should be used in the treatment of arthritis. In our opinion, after much experimentation with different curves, we have concluded that our best results were obtained with a fever of 104° F. sustained for eight hours. There is no danger should the fever rise to 105° F. or even 106° F. for a brief period; the important point to remember is not to allow it to fall below 104° F. during the treatment. Using this technic with the group of cases reported, 70 per cent were decidedly improved, and of these a few had remissions lasting from 12 to 21 months. An analysis of the data of those who reported poor results shows that they did not follow the technic that was suggested. Their patients were subjected to temperatures of 104° F. for a four-hour period or less, which we consider entirely inadequate treatment. With a control

* Received for publication March 6, 1934.

group,² using a similar technic, our results were likewise disappointing. It must also be borne in mind that our reported cases were selected from the intractable group that had failed to respond to any type of treatment, and, as we now include the less severe cases, our results are proportionately better. This, then, may serve to explain why we find some writers stating that they get good results with fever curves of lower level and of shorter duration. It may be that the milder cases show as marked an improvement with a fever treatment of 103.5° F. for a period of six hours as the more severe cases do with the higher fever (104° F.) sustained for eight hours.

The treatment should be given once weekly and the height and duration of the fever should always be determined by the condition of the patient. The number of treatments to be given will vary with the individual; one will need as few as eight while another may need as many as 20. Each patient presents an individual problem and must be prescribed for accordingly.

Warren and Wilson⁹ have reported excellent results in the treatment of gonorrheal vaginitis and cervicitis. No organisms could be demonstrated in many of their patients after one treatment. Those who failed to respond to the single fever treatment were subjected to a second, after which they, too, in most instances, were entirely free of gonococci and clinically all evidence of the disease had disappeared. Prior to the use of fever therapy, all of these cases were subjected and found resistant to the usual forms of treatment. They used a fever of 106.5° F. sustained for a five-hour period as a result of their *in vitro* experiments on the thermal death time of gonococci.^{10, 11} The second treatment, when necessary, was given 10 days to a month later.

Feinberg, Osborne and Afremow¹¹ in 1931 first introduced the use of hyperpyrexia in the treatment of intractable asthma and allergic diseases. In 1932 Feinberg, Osborne and Steinberg¹² summarized their results with 42 patients. They selected cases that had failed to respond to the usual methods of treatment and had been under their care for a few months to several years. These severe chronic asthmatics had one or more complicating pulmonary conditions such as emphysema, marked bronchitis or bronchiectasis. Although they do not advocate this treatment as a cure for asthma, yet they have noted complete remissions lasting from several days to 10 months in 51 per cent of this group; 29 per cent had improved but without remissions. They also pointed out that remissions may be delayed for two or three weeks after treatment and that their results should be more encouraging with less severe cases.

They advocate a fever of 104° F. for eight hours given at a four-day interval, two treatments constituting a course. When the patient's condition will not permit such a sustained fever, a temperature of 103.5° F. maintained for six hours still makes it possible to get a satisfactory result. The temperature should be kept below 105° F., although such a fever is not necessarily dangerous. The treatment should be given with the patient

sitting in bed, reclining on a back rest; however, those who are able to lie fully recumbent without discomfort are treated in that position. It is good practice to have ready a hypodermic syringe containing adrenalin so that it can be given without delay in case an attack is precipitated. Very cold or ice water should not be given during treatment because it too may induce an attack. In reviewing the indifferent results reported by some authors^{13, 14} in the treatment of asthma by electropyrexia, it is evident that they gave insufficient treatment.

Electropyrexia was first introduced by Neymann and Osborne¹⁵ in the treatment of dementia paralytica. The literature now contains the reports of 550 paretics that have been treated by electrically induced fever both here and abroad. A survey of these reports leads one to the conclusion that this form of therapy should eventually supersede the malarial method of treatment. Various authors have reported different remission rates. This, it would seem, points out the necessity of following a definite standardized technic.

First, the selection of patients is important. Best results can be expected only in the early cases of neurosyphilis before marked cellular destruction has taken place. Late deteriorated cases with marked cell destruction cannot be expected to respond. This point is well illustrated by reviewing the work of three investigators, namely, Neymann and Osborne,¹⁶ Simpson, Kislig and Sittler,⁶ and Freeman, Fong and Rosenberg.¹⁷ These articles are selected because they serve to show that unless a careful selection of patients is made, a uniform rate of remission will not be obtained.

Second, the fever should be maintained at a given height for a definite period of time. Bessemans¹⁹ has determined the thermal death time of *Treponema pallidum* both in vitro and in vivo. The more recent work of Boak, Carpenter and Warren²⁰ confirms the in vitro research of Bessemans. Neymann,¹⁸ therefore, advocates a fever above 103.5° F. for at least six hours, with an additional two hours at 105.8° F. Thus, the fever lasts for a period of at least eight hours. A temperature of 106° F. is permitted at any point during the treatment but is usually best tolerated at about the fourth hour. Treatments are given twice weekly, and usually, 20 treatments constitute a course.

The most extensive work in the treatment of multiple sclerosis by electropyrexia was done by Neymann and Osborne,²¹ who reported their results with 25 patients. They divided their cases into mild, advanced and far advanced. Forty-four per cent of the patients treated showed marked improvement, while an additional 40 per cent were improved to a lesser degree. They hold out but slight hope of improvement in the far advanced types. Such patients entail a risk in treatment that one is hardly justified in taking.

The temperature in multiple sclerosis should under no circumstances be permitted to exceed 105° F. due to the danger of upsetting the heat regulating mechanism and thus inducing heat stroke. A satisfactory fever for

these patients is 103.5° F. for a period of eight hours. The treatment should be terminated immediately, regardless of the duration of treatment, when the pulse exceeds 160 per minute, when the respiration is very rapid and shallow, or when marked cyanosis is present. With multiple sclerosis these danger signs call for very careful consideration and prompt action on the part of the physician. Treatment is given once a week, and the number required will vary but will probably average between 20 and 30.

At the present time many agents are advocated for raising body temperature, such as hot water baths, electric blankets, superheated air, electric light cabinets, radiotherms, diathermy, and a new device called the inductotherm, the latter device using the principle of electromagnetic induction. All of these, including foreign proteins, one of us (S. L. O.) has used and studied during the past five years. For a comparison of the relative merits of many of these methods one is referred to the work of Merriman and Osborne.²² In brief, all of the methods can be classified as either external or internal heating agents. The inductotherm, radiotherm and diathermy use electrical energy which is absorbed by the tissues and transferred into heat while the other agents merely conduct heat from the surface of the skin, and thus, by conduction, heat the underlying tissues. The slope of the normal physiological heat gradients of the body is not disturbed by the internal heating methods. With external applications to the body surface these normal heat gradients of the body are reversed.²³ Excessive heat to the surface of the body has a marked tendency to upset the heat regulating mechanism, thus causing heat stroke. Our experience leads us to favor the internally heating methods which do not reverse this natural heat gradient.

During the past year we have been working with an entirely new device called the inductotherm. This seems by far the most satisfactory apparatus introduced. In a paper by Holmquest and Osborne²⁴ data were presented on the heating of electrolytes by high frequency currents. Their research showed that the maximum heating effect in an electrolyte having the electrical conductivity of physiological salt solution was best secured by means of the inductotherm; second, the radiotherm; and third, by diathermy.

Johnson, Scupham and Gilbert²⁵ have demonstrated marked circulatory changes as shown by the finger pulse volume wave in the application of local heat as well as in fever induced by typhoid injections. It would seem that increased circulation may have a rather marked influence on the therapeutic results secured whenever fever is used, no matter from what source. These authors have also suggested that fever produced by foreign proteins is probably of central origin, while fever induced by other physical agents originates from the periphery. Studies now being conducted by Johnson, Osborne, Scupham and Coulter²⁶ tend to show that fevers of peripheral origin are probably more effective on the finger pulse volume wave than fevers produced by foreign proteins.

The newer developments in the technic are worthy of mention. For example, the use of a rectal electrical recording or indicating thermometer has become an absolute necessity and, in our opinion, the treatment cannot safely be given without it. The continuous temperature record constantly before one's eyes has eliminated many of the hazards due to the old method of periodic temperature reading. Likewise, the use of the new cuff electrode, devised by A. C. Jones of the University of Oregon Medical School, has added greatly to the comfort of the patient during treatment. Five electrodes are used, one around the trunk, one around each thigh, and one encircling each leg. These are hooked up to a special block from which a connection leads to the diathermy machine. They are easier to apply and

TABLE I
Summary of Technic

Disease	Fever Curve		Approximate Number of Treatments	Frequency of Treatments	Selection of Cases
	Degrees F.	Duration Hrs.			
Arthritis	104	8	8 to 20	Weekly	Infectious (rheumatoid, proliferative)
Gonorrheal Infection	106.5	5	1 or 2	2nd treatment from 10 to 30 days later	Vaginitis, cervicitis
Asthma	104	6 to 8	2	2nd treatment 3 days later	Intractable bronchial asthma
General Paresis.	103.5 for 6 then increase to 106 for 2		20	2 weekly	Early paretics and not too badly demented patients
Multiple Sclerosis	103.5 never above 105	8	20	Weekly	Not too far advanced

are of particular advantage with patients who have deformity of the back or chest where proper moulding cannot be secured with the larger jacket electrodes. The only disadvantage of the cuff method lay in the delicate construction of the material, necessitating frequent repairs. Kimble and Holmquest²⁷ have overcome this difficulty by the use of a new material which insures greater safety and durability. Again, the importance of a proper conducting lubricant can only be appreciated by those who have had considerable experience with electropyrexia. The "hot spots" and superficial scalds so frequently observed have been proved to be due in many cases to the lubricant used. Kimble and Holmquest,²⁸ after much investigation, have developed a conducting jelly which decreases materially this distressing occurrence. The patient's discomfort has been still further

lessened by the use of a special zipper-type treatment bag² which eliminates the excessive weight of blankets necessary for proper heat insulation.

During the treatment the tremendous fluid loss²² with the associated loss of chloride is partially replaced by liberal amounts of water containing six grams of sodium chloride to the liter. This procedure undoubtedly lessens the vomiting and the muscle cramps which result from the chloride loss,⁶ estimated at between 20 to 26 grams during each treatment. For the restlessness at the height of the fever, morphine sulphate (gr. $\frac{1}{4}$) hypodermically has been found superior to all other sedatives tried. Chloral hydrate recommended by Warren and Wilson⁹ proved disappointing to us, and hyoscine²¹ is dangerous because it inhibits the secretion of sweat. Furthermore, calmness on the part of the personnel as well as the elimination of unnecessary noises and lights tends to lessen the fears of the patient.

In conclusion, it must be kept in mind at all times that one is treating a patient rather than a disease. The fever curves suggested in table 1 should be maintained, if possible, but must be modified to meet the individual reactions that occur; with the diathermy method such adjustments can be easily and rapidly made. Obviously, until one is familiar with the technic, only patients offering the least possible risk should be selected.

REFERENCES

1. MARKSON, D. E., and OSBORNE, S. L.: The treatment of arthritis by sustained fever therapy; preliminary report of six cases, *Illinois Med. Jr.*, 1931, ix, 397-403.
2. MARKSON, D. E., and OSBORNE, S. L.: The treatment of arthritis by electropyrrexia, *Illinois Med. Jr.*, 1933, lxiv, 231-237.
3. MARKSON, D. E., and OSBORNE, S. L.: The treatment of chronic infectious arthritis by electropyrrexia. (Read before the American Congress of Physical Therapy, Chicago, Sept. 14, 1933.)
4. BISHOP, F. W., HORTON, C. B., and WARREN, S. L.: A clinical study of artificial hyperthermia induced by high frequency currents, *Am. Jr. Med. Sci.*, 1932, clxxxiv, 515-533.
5. AUCLAIR, E., WEIL, et al.: Discourse rapports et communications sur l'electropyrrexia soiree d 15 Juin, 1932, Paris, France.
6. SIMPSON, W. M., KISLIG, F. K., and SITTLER, E. C.: Ultrahigh frequency pyretotherapy of neurosyphilis; preliminary report, *ANN. INT. MED.*, 1933, vii, 64-75.
7. TENNEY, C. F.: Artificial fever produced by short wave radio and its therapeutic application, *ANN. INT. MED.*, 1932, vi, 457-468.
8. NICHOLS, E. H., and RICHARDSON, F. L.: Arthritis deformans, *Jr. Med. Res.*, 1909, xxi, 149-221.
9. WARREN, S. L., and WILSON, K. M.: The treatment of gonococcal infections by artificial (general) hyperthermia; preliminary report, *Am. Jr. Obst. and Gynec.*, 1932, xxiv, 592-598.
10. CARPENTER, C. M., BOAK, R. A., MUCCI, L. A., and WARREN, S. L.: Studies on physiologic effects of fever temperatures; thermal death time of *Neisseria gonorrhoeae* in vitro with special reference to fever temperatures, *Jr. Lab. and Clin. Med.*, 1933, xviii, 981-990.
11. FLINBLAD, S. M., OSBORNE, S. L., and AFREMOV, M. L.: A new method of nonspecific treatment of allergic disease, preliminary report, *Jr. Allergy*, 1931, ii, 291-293.
12. FLINBLAD, S. M., OSBORNE, S. L., and STEINBERG, M. J.: Sustained artificial fever in treatment of intractable asthma; physiologic and therapeutic considerations, *Jr. Am. Med. Assoc.*, 1932, xcix, 801-806.

13. LEOPOLD, S. S., and STEWART, S. G.: Effects of fever, either accidentally incurred or artificially produced, in bronchial asthma, Jr. Allergy, 1931, ii, 425-435.
14. MILLER, H., and PINESS, G.: Hyperthermia induced by high frequency electric current in treatment of intractable asthma, Jr. Allergy, 1931, ii, 436-443.
15. NEYMANN, C. A., and OSBORNE, S. L.: Artificial fever produced by high frequency currents; preliminary report, Illinois Med. Jr., 1929, lvi, 199-203.
16. NEYMANN, C. A., and OSBORNE, S. L.: Treatment of dementia paralytica with hyperpyrexia produced by diathermy, Jr. Am. Med. Assoc., 1931, xcvi, 7-13.
17. FREEMAN, W., FONG, T. C., and ROSENBERG, S. J.: Diathermy treatment of dementia paralytica; microscopic changes in treated cases, Jr. Am. Med. Assoc., 1933, c, 1749-1753.
18. NEYMANN, C. A.: Principles and practice of physical therapy, 1932, W. F. Prior Co., Inc., Hagerstown, Maryland, Vol. I, Chapter 17.
19. BESSEMAN, A., and THIRY, U.: Nouveaux essais d'application de la thermothérapie locale au traitement de la syphilis primaire et secondaire chez l'homme, Bruxelles-méd., 1933, xiii, 299.
20. BOAK, R. A., CARPENTER, C. M., and WARREN, S. L.: Studies on physiological effects of fever temperatures; thermal death time of *Treponema pallidum* in vitro with special reference to fever temperatures, Jr. Exper. Med., 1932, lvi, 741-750.
21. NEYMANN, C. A., and OSBORNE, S. L.: The treatment of some multiple sclerosis by electropyrexa, Jr. Nerv. and Ment. Dis. (To be published.)
22. MERRIMAN, J. R., and OSBORNE, S. L.: Methods of producing hyperpyrexia by various physical agents, Illinois Med. Jr., 1933, lxiv, 237-240.
23. NEYMANN, C. A., and OSBORNE, S. L.: The physiology of hyperpyrexia, Am. Jr. Syphilis. (To be published.)
24. HOLMQUEST, H. J., and OSBORNE, S. L.: The heating of electrolytes by high frequency currents. (Read before the American Congress of Physical Therapy, September 1933.)
25. JOHNSON, C. A., SCUPHAM, G. S., and GILBERT, N. C.: Studies on peripheral vascular phenomena; observations on peripheral circulatory changes following unilateral cervical ganglionectomy and ramisectomy, Surg., Gynec. and Obst., 1932, lv, 737-741.
26. JOHNSON, C. A., OSBORNE, S. L., SCUPHAM, G. S., and COULTER, J. S.: Personal communication.
27. KIMBLE, H. E., and HOLMQUEST, H. J.: Diathermy electrode based on entirely new principles, Illinois Med. Jr., 1933, lxiv, 550-552.
28. KIMBLE, H. E., and HOLMQUEST, H. J.: Rôle of electrode compounds in preventing diathermy burns, Arch. Phys. Therapy, 1933, xiv, 669-671.

HEMATOLOGICAL RESPONSE OF ADDISONIAN PER- NICIOUS ANEMIA TO BREWER'S YEAST *

By HOLLIS K. RUSSELL, M.D., *Valhalla, N. Y.*

RECENTLY Strauss and Castle¹ postulated that Addisonian pernicious anemia is due to the lack of a specific (hematopoietic) reaction between an extrinsic, dietary factor (vitamin B₂), and an intrinsic factor present in normal gastric juice. In Addisonian anemia the lack of the specific reaction is due to an absence of intrinsic factor, and the extrinsic factor alone will not produce a hematological response. We have tested this theory on four cases of Addisonian pernicious anemia and the results form the basis of this report.

OUTLINE OF TECHNICAL PROCEDURE

After the diagnosis of Addisonian pernicious anemia was established these patients were placed on the regular ward diet without liver for a control period varying from three to five days in order to establish the level of the reticulocytes prior to beginning treatment. After this had been accomplished all four patients were given brewer's yeast (a rich source of vitamin B₂), beginning with one drachm three times a day and increasing in three days to two drachms thrice daily. The reticulocytes were followed daily to note any hematological response. During the time of administration of the yeast the patients received the regular ward diet without liver. After the response obtained by feeding yeast began to recede (except case 2), three cubic centimeters of parenteral liver extract were given on each

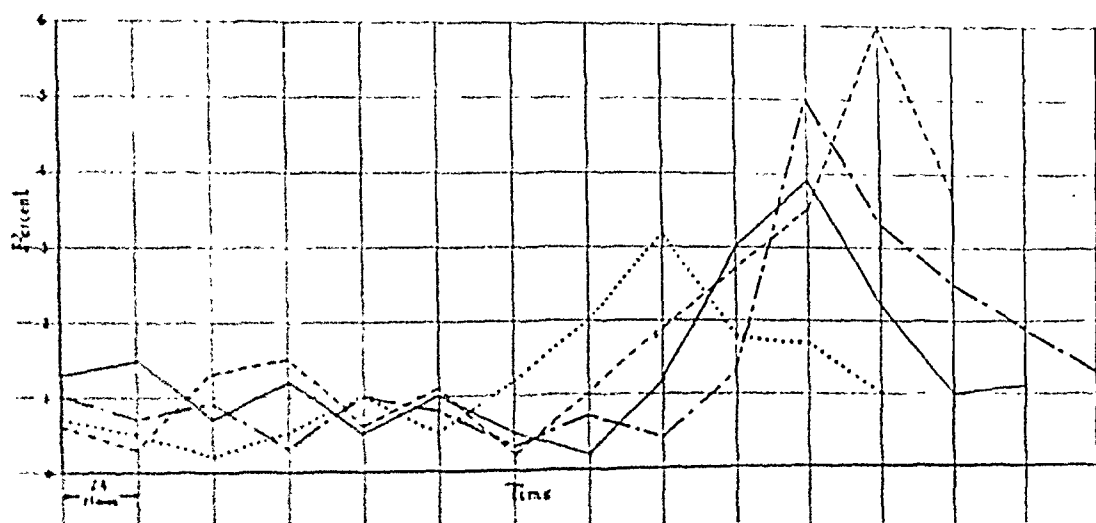


FIG. 1. Graph showing the reticulocyte response to brewer's yeast in the four cases that are reported. The starting points of the lines of the graph indicate the cases in the following order, reading from the bottom upward: Case 2, 4, 1 and 3.

* Received for publication January 26, 1934.
From the laboratory of Grasslands Hospital.

of three successive days and the reticulocytes followed with daily observations to determine the type of hematological response. Red corpuscle counts and hemoglobin estimations were made at intervals of 48 to 72 hours during the course of the experiment.

As seen by the graph, there occurred in all four cases a slight but definite reticulocyte response after brewer's yeast was added to the diet. This increase in reticulocytes occurred in five to seven days and the intensity of the response varied between 3.2 per cent and 6 per cent. Following the administration of parenteral liver extract a second response occurred of much greater intensity and duration. The intensity of this response varied between 12 per cent (in one case in which the red corpuscle level was 2.9 million) and 26 per cent. Prior to adding brewer's yeast to the diet the reticulocytes in all four cases averaged 0.8 per cent and were never above 1.7 per cent.

CASE I

S. L., aged 70 years, white, female, widow, American. Diagnosis: Addisonian pernicious anemia. Admitted 3/30/33; discharged 4/29/33.

Brief Summary. Number of relapses: three. Previous treatment: liver diet with adequate response. First became anemic three years ago.

Chief Complaints. Weakness, dyspnea, numbness of legs and feet.

Positive Physical Findings. Skin showed a yellowish waxy pallor, smooth tongue, impairment of vibratory sense over lower extremities.

Laboratory Data. Urine: no abnormal constituents except positive urobilinogen 1-20. Blood Wassermann, negative. Chemistry: non-protein nitrogen 31.2 mg.; creatinine 1.5 mg.; sugar 125 mg.; icteric index 16.6. Red blood corpuscles 2,800,000; hemoglobin 46 per cent (Newcomer); white blood cells 3,150; volume index 1.46 (hematocrit).

The red corpuscles were well filled with hemoglobin and showed a predominance of oval macrocytes. Few poikilocytes.

Gastric analysis: Free hydrochloric acid absent in all fractions.

Course. Excellent hematological response. Discharged as improved 30 days after admission.

CASE II

W. K., aged 60 years, white, male, single, American, laborer. Diagnosis: Addisonian pernicious anemia. Admitted 2/6/33. Discharged 3/25/33.

Brief Summary. Number of relapses: one. First became anemic six months ago.

Chief Complaints. Substernal pain, edema of ankles, epigastric distress, numbness of hands and feet and diarrhea. These appeared gradually during the past six months.

Positive Physical Findings. Skin showed an icteric pallor, petechial hemorrhages arms and hands, smooth tongue, and loss of vibratory sense below knees.

Laboratory Data. Urine: no abnormal constituents except positive urobilinogen, dilution 1-30. Blood Wassermann, negative. Blood chemistry: icteric index 40; red blood corpuscles 1,360,000; hemoglobin 34 per cent (Newcomer); white blood cells 4,400; color index 1.3; volume index 1.9 (hematocrit).

The red corpuscles were well filled with hemoglobin and showed a predominance of oval macrocytes. Numerous poikilocytes and a few erythroblasts were present.

Gastric analysis showed a low total acidity and no free hydrochloric acid in any of the fractions.

Course. Excellent hematological response. Patient discharged as improved 47 days after admission.

CASE III

W. T., aged 66 years, white, male, married, American, salesman. Diagnosis: Addisonian pernicious anemia. Admitted 4/2/33. Discharged 6/5/33.

Brief Summary. Number of relapses: four. Previous treatment: liver diet first, two relapses; parenteral liver extract last, two relapses. First became anemic three and one-half years ago.

Chief Complaints. Weakness, shortness of breath, pallor and numbness of hands, failing eyesight.

Positive Physical Findings. Skin a yellowish pallor, smooth tongue, impaired vibratory sense below the knees.

Laboratory Data. Urine: contained a trace of albumin and urobilinogen in 1-30 dilution. There were no other abnormal constituents. Blood Wassermann, negative. Blood chemistry: icteric index 11.1; red blood corpuscles 1,900,000; hemoglobin 39 per cent (Newcomer); volume index 1.29 (hematocrit).

The red corpuscles showed a predominance of oval macrocytes and a few poikilocytes. Eye consultation revealed early degeneration of the retina. Gastric analysis showed a low total acidity with no free hydrochloric acid in any of the fractions.

Course. Excellent hematological response. Eye condition improved rapidly as his general condition improved. Discharged as improved 37 days after admission.

CASE IV

A. W., aged 52 years, white, female, married, American, housewife. Diagnosis: Addisonian pernicious anemia. Admitted 3/2/33. Discharged 4/13/33.

Brief Summary. Number of relapses: one. Previous treatment: liver diet. First became anemic three and one-half years ago.

Chief Complaints. Epigastric distress, attacks of diarrhea, periodic burning of tongue, weakness, marked ataxia and inability to use legs.

Positive Physical Findings. Skin a lemon color, tongue smooth, ataxic movements of hands and feet, loss of vibratory sense from mid-thigh downward. Skin anesthesia from sacrum downward.

Laboratory Data. Urine: no abnormal constituents. Blood Wassermann, negative. Blood chemistry: icteric index 12.5; red blood corpuscles 1,300,000; hemoglobin 25 per cent (Newcomer); white blood cells 4,200; volume index 1.36 (hematocrit).

Morphology of red corpuscles: Predominance of oval macrocytes, many poikilocytes, slight polychromasia. Gastric analysis: Low total acidity with no free hydrochloric acid in any fraction.

Course. Excellent hematological response. Hospital days 21.

DISCUSSION

Judging by the increase in reticulocytes, generally accepted as a guide to the efficacy of treatment in Addisonian anemia,² all four cases responded to brewer's yeast. While the therapeutic importance of our results seems slight, yet they are interesting because definite hematological response followed the sole administration of Castle's extrinsic factor. We intend to test the limitation of "extrinsic factor" alone in maintaining remissions.

TABLE I
Blood Response of Addisonian Anemia to Brewer's Yeast and Parenteral Liver Extract

Day of Treatment	Case I (March 31-April 19, 1933)				Case II (March 7-26, 1933)				Case III (April 3-22, 1933)				Case IV (March 3-22, 1933)			
	Treatment	Re-ticu- locyte per cent	Red cor- pus- cles in mil- lions	Hgb. in per cent	Treatment	Re-ticu- locyte per cent	Red cor- pus- cles in mil- lions	Hgb. in per cent	Treatment	Re-ticu- locyte per cent	Red cor- pus- cles in mil- lions	Hgb. in per cent	Treatment	Re-ticu- locyte per cent	Red cor- pus- cles in mil- lions	Hgb. in per cent
1	H.D.*	1.0	2.80	46	H.D.*	0.6	1.36	34	H.D.*	1.3	1.90	39	H.D.*	0.7	1.30	30
2	"	1.7	"	0.3	"	1.5	"	0.5
3	"	0.9	"	1.3	"	0.7	1.75	40	"	0.2
4	"	0.4	"	1.5	1.45	31	H.D.*	1.2	Plus B.Y.†	0.6	1.09	28
5	H.D.*	1.0	2.17	47	H.D.*	0.6	Plus B.Y.†	0.5	1.61	36	"	1.0
6	Plus B.Y.†				Plus B.Y.†				"				"			
7	"	0.8	"	1.1	1.50	33	"	1.0	"	0.5	1.01	29
8	"	0.3	2.51	48	"	0.2	"	0.5	"	1.2
9	"	0.7	"	1.0	"	0.2	1.93	35	"	2.0	0.94	23
10	"	0.4	"	1.9	1.21	30	"	1.2	" T.‡	3.2
	"	1.3	1.91	44	"	2.7	"	3.0	1.80	33	H.D.*	1.8
11	"	5.0	"	3.5	"	3.9	Plus B.Y.†			
12	"	3.3	1.85	45	H.D.*	6.0	1.61	31	H.D.*	2.2	2.05	38	Plus P.†	1.7	1.81	30
13	H.D.*	2.5	Plus P.†	3.7	Plus P.†	1.0	"	1.0
14	"				"				"				H.D.*	5.0	1.85	35
15	"				"				"				Plus B.Y.†			
16	H.D.*	1.9	H.D.*	9.1	"	1.1	"	16.2
	Plus B.Y.†	1.3	2.45	44	Plus B.Y.†	12.8	2.40	39	H.D.*	4.9	2.25	39	"	26.0	2.21	34
17	"	0.5	"	15.7	Plus B.Y.†	15.0	"	20.1
18	"	4.4	"	6.2	2.75	41	"	21.3	2.50	45	"	14.0	1.99	30
19	"	3.9	2.00	44	"	3.7	"	13.3	"	10.5
20	"	12.0	"	1.5	"	5.0	"	12.5
	"	7.5	2.61	51	"	0.5	3.0	50	"	2.6	3.01	53	"	3.1	2.58	40

* H.D. Hospital diet without liver.

† B.Y. Brewer's yeast.

‡ P. Parenteral liver extract.

§ T. Transfusion (300 c.c. whole blood).

From the results as outlined one of the following conclusions seems unavoidable:

1. That the gastric secretions of these four cases of Addisonian anemia contained some intrinsic factor but insufficient to prevent symptoms of the disease, or

2. That small amounts of the specific product of extrinsic and intrinsic factors were present and administered in the brewer's yeast, or were present in all four of the patients (possibly stored in the body due to previous treatment), in amounts insufficient to prevent symptoms and were activated by the large amounts of yeast which these patients received, or

3. Castle's explanation is not correct and small amounts of extrinsic factor (brewer's yeast) alone are capable of stimulating hematopoiesis.

It seems likely that many cases of Addisonian pernicious anemia contain lesser amounts of the intrinsic factor than are necessary to prevent the development of the disease but are not entirely devoid of it. The symptoms are then the result of a quantitative rather than an absolute lack of the factor. Spontaneous remissions, which are a characteristic of the disease, would seem to indicate this must be true. Such a partial deficiency may have been present in the four cases here reported and their response may have been the result of such a mechanism as Castle postulated.

CONCLUSION

Four typical cases of Addisonian pernicious anemia are reported in which a reticulocyte response followed the administration of brewer's yeast (extrinsic factor of Castle).

The author wishes to express his appreciation to Dr. Gilbert Dalldorf and Dr. Joseph Connery for valuable suggestions in the preparation of this paper.

REFERENCES

1. STRAUSS, M. B., and CASTLE, W. B.: Nature of extrinsic factor of deficiency state in pernicious anemia and in related macrocytic anemias; activation of yeast derivatives with normal human gastric juice, *New England Jr. Med.*, 1932, ccvii, 55-59.
2. MURPHY, W. P., MONROE, R. T., and FITZ, R.: Changes in composition of blood in pernicious anemia treated by diet rich in liver, *Jr. Am. Med. Assoc.*, 1927, lxxxviii, 1211-1214.

EXTERNAL TRAUMA IN RELATION TO ULCER OF THE STOMACH AND DUODENUM *

REPORT OF FIVE CASES

By IRVING GRAY, M.D., F.A.C.P., *Brooklyn, N. Y.*

DESPITE the fact that our knowledge of the pathogenesis of peptic ulcer still remains in the field of theoretical discussion, we are occasionally called upon to decide whether or not injury to the upper abdomen can lead to the formation of a peptic ulcer. Theoretically it would appear that a strong blunt force suddenly applied to the epigastric area might lead to changes within the gastric wall and subsequently to the production of ulcer. The finding of an ulcer after such injury raises the question: Did the trauma act in the nature of the precipitating cause or did the trauma act in the nature of a revealing incident of preëxisting disease?

LITERATURE

In reviewing the American literature on the subject there is a paucity that is quite striking when one considers the importance of this subject.

Recently Crohn and Gerendasy,¹ reported a case of traumatic ulcer of the duodenum. A brief review of their case is as follows: A woman, aged 45, was forcibly struck in the epigastrium. A tarry stool was noted twenty-four hours later and forty-eight hours after the accident the patient vomited blood. Subsequently the patient developed symptoms strongly suggestive of duodenal ulcer, and roentgen studies taken a month after the accident and again a year later showed a definite deformity of the duodenal bulb. Two years after the injury the patient still presented all the features of a true duodenal ulceration.

Eusterman and Mayo,² at the meeting of the American Gastro-Enterological Association in 1932, reported a case of acute peptic ulcer in a boy, aged 16 years, who had fallen head-long from the back of a moving automobile, striking the epigastrium forcibly on an empty spare tire rack. The accident happened in October 1931, and he was first seen at the Mayo Clinic in March 1932. "At the time of the accident he had experienced no actual pain, although there was some contusion of the upper left abdominal wall and he did not feel well for the remainder of the day. Within twenty-four hours epigastric pain appeared and was most marked on exertion, so that he eventually was compelled to discontinue all work, attendance at school and participation in sports. Aggravation of the pain was not caused by taking food. Shortly after the injury he had had occasional left epigastric pain which appeared half an hour to an hour after meals, lasted for an

* Address to the Society for the Advancement of Gastro-Enterology, New York, N. Y., Dec. 27, 1933.

hour or so and disappeared before the next meal, so that he was always free of pain at meal time. Five months had passed since the injury, the above symptoms persisting off and on, when, after a heavy day's work on the farm, he had recurrence of epigastric pain and noticed tarry stools. On the two following days he was free of pain. Then the pain became more marked and was associated with the first, massive hemorrhage from the stomach, syncope and shock. Following this hemorrhage the pain disappeared and the boy was brought to the clinic.

"Roentgenoscopic examination, March 21, 1932, gave clear evidence of a penetrating ulcer on the lesser curvature, above the incisura angularis. Three days later, after administration of histamine, there was a great deal of secretion, maximal total acidity was 106 units, and free hydrochloric acid, 94 units (titration with tenth normal sodium hydroxide). Because the patient was young and the symptoms of recent onset, operation was deferred and intensive treatment undertaken. He was placed in the hospital and made a favorable response. Successive roentgenographic examinations disclosed gradual diminution in the niche, and April 16, 1932, no defect was demonstrable. The boy was dismissed to follow a regimen of ambulant patients with ulcer. He has been so well since that time that we have not been able so far to get him to return for reexamination, although he lives just across the border in a neighboring state.

"The fact that the usual type of chronic gastric ulcer is uncommon in youths, and that the ulcer promptly disappeared under treatment, tends to support our opinion that the lesion was of recent and traumatic origin."

The foreign literature, especially the French and the German, is replete with illustrative cases and references on the subject of traumatic ulcer. In discussing gastric injuries following strong blunt force, Rehn³ divided these injuries into:

1. Tears of the serous coat.
2. Injuries to the serous-muscular coat.
3. Separation by hematoma formation between the muscular layers and the mucosa.
4. Tears of the mucosa.
5. Penetrating ruptures.

Stern⁴ adds a sixth type of injury, namely, compression of the stomach not resulting in macroscopic tears.

Petit⁵ reported 73 cases of traumatic gastric ulcer. In his series the diagnosis was based upon history of accident and gastric symptoms, especially gastric hemorrhage. In the absence of roentgen-ray confirmatory evidence the diagnosis of traumatic ulcer is open to serious question.

Duplay,⁶ Leube,⁷ and M. Strauss⁸ have each reported individual cases of traumatic peptic ulcer. In each instance the patient made an uneventful recovery and the diagnosis was based on clinical symptomatology and not confirmed by roentgen-ray.

A review of the entire foreign literature is contained in the third edition of Richard Stern's ⁹ textbook. The first case in which the origin of gastric ulcer was attributed to abdominal injury was published by Potain,¹⁰ in 1856. The onset of clinical symptoms, in a woman of 60 years, immediately after she had received an abdominal injury, the persistence of gastric symptoms for eight years and autopsy confirmation of an ulcer on the lesser curvature penetrating into the pancreas, all combined to make the diagnosis of a traumatic gastric ulcer probable.

EXPERIMENTAL PRODUCTION OF PEPTIC ULCER BY TRAUMA

Animal experimentation was done by Ritter,¹¹ Vanni¹² and Gross,¹³ to see if gastric ulcer could be produced by external trauma. Ritter struck a dog with a hammer in the gastric region and four days later at autopsy found a hemorrhagic elevation of the mucous membrane the size of a quarter. This elevation was surrounded by an extravasation of blood. Microscopical examination showed a separation of the mucosa and submucosa by an hematoma. Ritter concluded that the peptic action of gastric juice would have produced an ulcer in a short time. This question is open to a great deal of doubt, for in subsequent animal experiments of similar nature Quincke and Daettwyler,¹⁴ Griffini and Vassale¹⁵ and Matthes,¹⁶ and others showed that the mucous membrane injuries healed quickly.

In experimental work done on rabbits, Vanni¹² proved that when the animal's stomach was filled with food, trauma readily produced tears and hemorrhage of the mucosa and submucosa. In a second experiment, repeated daily injuries to the area of the stomach filled with food showed in some animals hemorrhages in the mucosa and submucosa one to three weeks after the injury and in others nothing abnormal was found. In a third series of experiments, in rabbits that had not been fed for three days, this author found in one animal out of six, evidence of a localized ulceration after severe injury to the stomach area. These experiments were repeated by Gross,¹³ whose findings were in the main similar to those of Vanni.

Although these experiments were rather crude and in no instance was a true ulcer produced, nevertheless it was shown that when the stomach was full, tears of the mucous membrane and hemorrhage into the walls of the stomach were more frequent than when the stomach was empty and further that the natural tendency after such trauma was toward healing.

CASE REPORTS OF TRAUMATIC ACUTE PEPTIC ULCER

CASE I

A female adult of 31 was in a taxicab collision in March 1932. She could not remember the exact details of her abdominal injury but stated that she received severe contusions of the upper abdomen. Within 24 hours after the accident she began vomiting blood and noticed that her stools were tarry. For a period of two weeks after the accident hematemesis would occur almost daily and the stools were con-

tinuously black. She had frequent abdominal pain and distress after meals. The patient denied ever having had any gastric complaints prior to her accident. Roentgen-ray examination, 17 days after the injury, showed a defect in the region of the pylorus and a defect in the duodenal cap with a minimum gastric residue at the end of six hours. The subjective symptoms of pain immediately after the intake of food with occasional vomiting and tenderness in the upper epigastrium persisted for almost a year after the accident, when the patient first came under my observation. A second fluoroscopic and roentgen-ray study of the stomach had been made nine months after the original study and both the stomach and the duodenal bulb were reported as being normal. The six hour study showed a small residue in the pyloric end of the stomach. When I saw the patient approximately one year after the accident she was still complaining of distress after meals and occasional attacks of vomiting. The physical examination was essentially negative except for tenderness in the epigastrium and a slight secondary anemia. Repeated examination of the stool failed to show occult blood. A fluoroscopic and roentgen-ray examination of the gastrointestinal tract was entirely negative except for a colonic hyper-motility at the end of six hours. There was no gastric residue present at this examination.

CASE II

A male adult of 37, who had never had previous digestive complaints, sustained an injury to the epigastrium in the spring of 1933, when he was forcibly struck by a wooden plank. Within 24 hours he began to complain of epigastric pain with discomfort after meals and occasional vomiting. There was no hematemesis. Roentgen-ray study, one month after the accident, revealed a persistent irregularity on the mesial aspect of the duodenal bulb. His subjective symptoms gradually abated and when I saw him three months after his accident the only finding, on examination, was tenderness in the right epigastric area. Roentgen-ray study, at this time, showed a normal stomach and duodenal bulb. Re-examination two months later confirmed the finding of a normal stomach and duodenum. The gastric symptoms had entirely subsided.

CASE III

A male adult, 41 years of age, in January 1932, received a crushing injury to the upper abdomen when he was caught between the steering wheel and the body of a truck, in an automobile accident. The accident occurred about one-half hour after the noon-day meal. Within a few hours he began to complain of persistent dull pain in the epigastrium. This dull pain continued for several weeks and was associated with discomfort after meals. There was no vomiting but during the first weeks after his accident the stools were tarry. Roentgen-ray studies of the stomach, three weeks after the injury, were reported as negative. There was persistent gastric distress, and a second examination done two months after the accident showed evidence strongly suspicious of an ulcer on the lesser curvature of the stomach. A third roentgen-ray study four months later showed no evidence of a gastric ulcer, but the report stated that there was marked increase in tonus and peristaltic activity. At the end of four hours the stomach was entirely empty and the head of the barium meal was in the sigmoid. I first saw this patient seven months after his accident because of the continued distress after eating even the simplest foods. Other than slight tenderness in the epigastrium the examination was entirely negative. The roentgen-ray study showed no evidence of gastric or duodenal disease.

These cases are reported as examples of acute traumatic peptic ulcer running a short course. The roentgen-ray findings associated with the presence of blood in the stool during the first week after the accident (case

3) were strongly indicative of an acute traumatic peptic ulcer. The aforementioned three cases are classified as "acute traumatic peptic ulcer with recovery" in view of the history of accident, the clinical progress and the roentgen findings.

Peptic ulcer following trauma and confirmed by autopsy has been reported in recent years.

Fertig¹⁷ cites the case of a young man aged 28, who was kicked in mid-abdomen by a horse. Operation two and one-half hours after the accident seemed imperative. The abdomen was opened but no lesion of the stomach could be discovered. Several weeks later death occurred due to excessive hematemesis. Postmortem examination revealed the presence of four small ulcers on the lesser curvature. An eroded artery in the depths of the largest ulcer was held to be responsible for the massive hemorrhage which caused death.

A young man of 21 was knocked down by a bull and kicked in the right side of the thorax and abdomen. The patient was observed by Hausbrandt,¹⁸ who investigated the case not only clinically but also histologically. Immediately after the accident this young man developed intense pain in the epigastrium and board-like rigidity of the abdomen. An operation was performed on the following day which showed a rupture of the left hepatic lobe. The liver was sutured and drained. On the subsequent days, there was pain in the abdomen and sensitiveness to pressure, especially on the right side. When the gauze was removed from the drain, bile flowed out freely. Assuming the presence of a biliary peritonitis, Hausbrandt made another laparotomy and found that the bile came from beneath the liver out of a gap in the lesser omentum. The liver suture was intact. Four days later the patient died of bronchopneumonia. An autopsy revealed a blood clot the size of a fist and some liquid blood in the stomach. On the antero-posterior surface of the stomach, three large and several small ulcers were found which were irregularly distributed and had jagged edges. The mucosa which had a blackish, brownish friable base, projected over these ulcers. The lesser curvature and pyloric region were devoid of them. Histological examination showed that these ulcers extended into the submucosa, which was thickened to two and one-half times its normal size. There was a great deal of cellular infiltration and several small hematomas. The bases of the ulcers were densely infiltrated with leukocytes and the upper layers reduced to fibers. In one ulcer, three cross-sections of the artery were seen to lead toward the base with walls densely infiltrated with leukocytes. The lumen contained thrombi which were rich in leukocytes. The bases of the two ulcers contained a brownish pigment. Hausbrandt believes that the ulcers arose from bruising of the gastric mucosa with consequent digestion of the injured part and sloughing through demarcation.

As evidence of the rapidity with which ulcer formation in the duodenum may occur following trauma the case reported by Gruber¹⁹ is of great interest. A man of 39 was struck by a falling body and died 60 hours later

from injuries to the abdominal thoracic organs. At autopsy a fresh bleeding acute ulcer was found in the duodenum.

CHRONIC PEPTIC ULCER CAUSED BY TRAUMA(?)

CASE IV

In October 1931, a man, aged 28 years, forcibly struck his upper abdomen against the edge of a table. Within a few hours after this accident he began to vomit and had persistent epigastric pain. Examination shortly after injury showed evidence of a contusion of the muscles in the epigastric region with abrasions of the skin. Pain

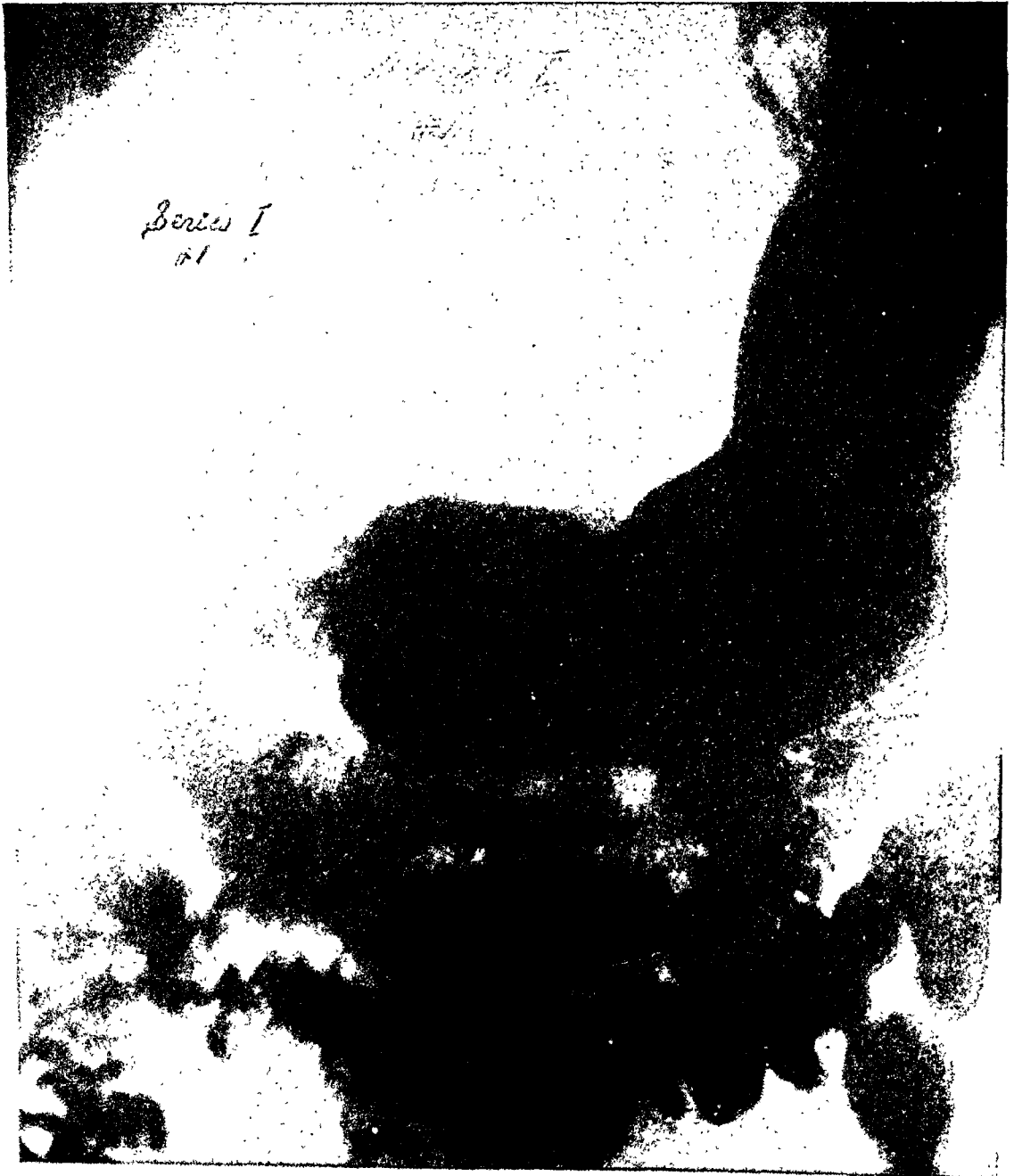


FIG. 1. Series I. Number 1.

was almost constant and was aggravated for the first few weeks by the intake of food. The vomitus did not contain any blood and occurred after meals. Six weeks after the injury a roentgen-ray study showed definite and persistent deformity of the duodenal bulb with a minimal gastric six hour residue. Gastric symptoms persisted and at the end of four months when the patient first came under my observation he presented a typical symptom complex of a duodenal ulcer. The intake of food would relieve the pain. Within one to two hours pain would recur and was again relieved by food or alkali medication. There was no previous history of any gastric disturbances. This man was seen by me at frequent intervals for a period of 18 months. Repeated roentgen study showed a characteristic deformity of the duodenal bulb. At times there was a persistent niche on the lesser curvature of the bulb highly suggestive of

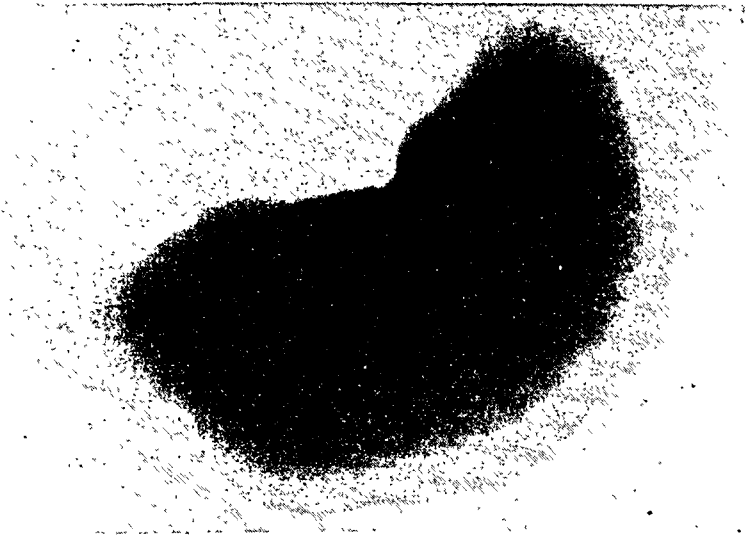


FIG. 2. Series II.

a penetrating ulcer. At times the symptoms were such as to suggest impending perforation. The pain was quite marked and the epigastric tenderness persisted. Pain in the back, in the region of the lower thoracic vertebrae, suggested the possibility of penetration into the pancreas. Operation was refused.

In reporting this case as one of chronic duodenal ulcer caused by trauma a question mark was placed after the word trauma because it is difficult to state whether trauma produced the ulcer or acted as an aggravating factor of preëxisting ulcer disease. There was no previous history of gastric disturbances but of course the absence of symptoms does not preclude the presence of a preëxisting ulcer. This man was hyper-sensitive to pain by the styloid pressure test of Libman,²⁰ and in view of the work reported by Crohn²¹ on pain sensitivity in relation to ulcer it would appear reasonable to state that if this man had had a duodenal ulcer prior to his accident he would have manifested symptoms of his disease. When I saw the patient, however, the factor of compensation played so important a part that it was difficult correctly to evaluate the degree of sensitivity.

The question in this case is whether or not the single trauma which this man sustained initiated the pathological process which led to ulcer formation or whether a latent ulcer was aggravated and became active. This question is all important; for in the settlement of each case much depends on whether or not injury produced or aggravated the existing process. The adjudication of traumatic ulcer is made difficult by the fact that peptic ulcer

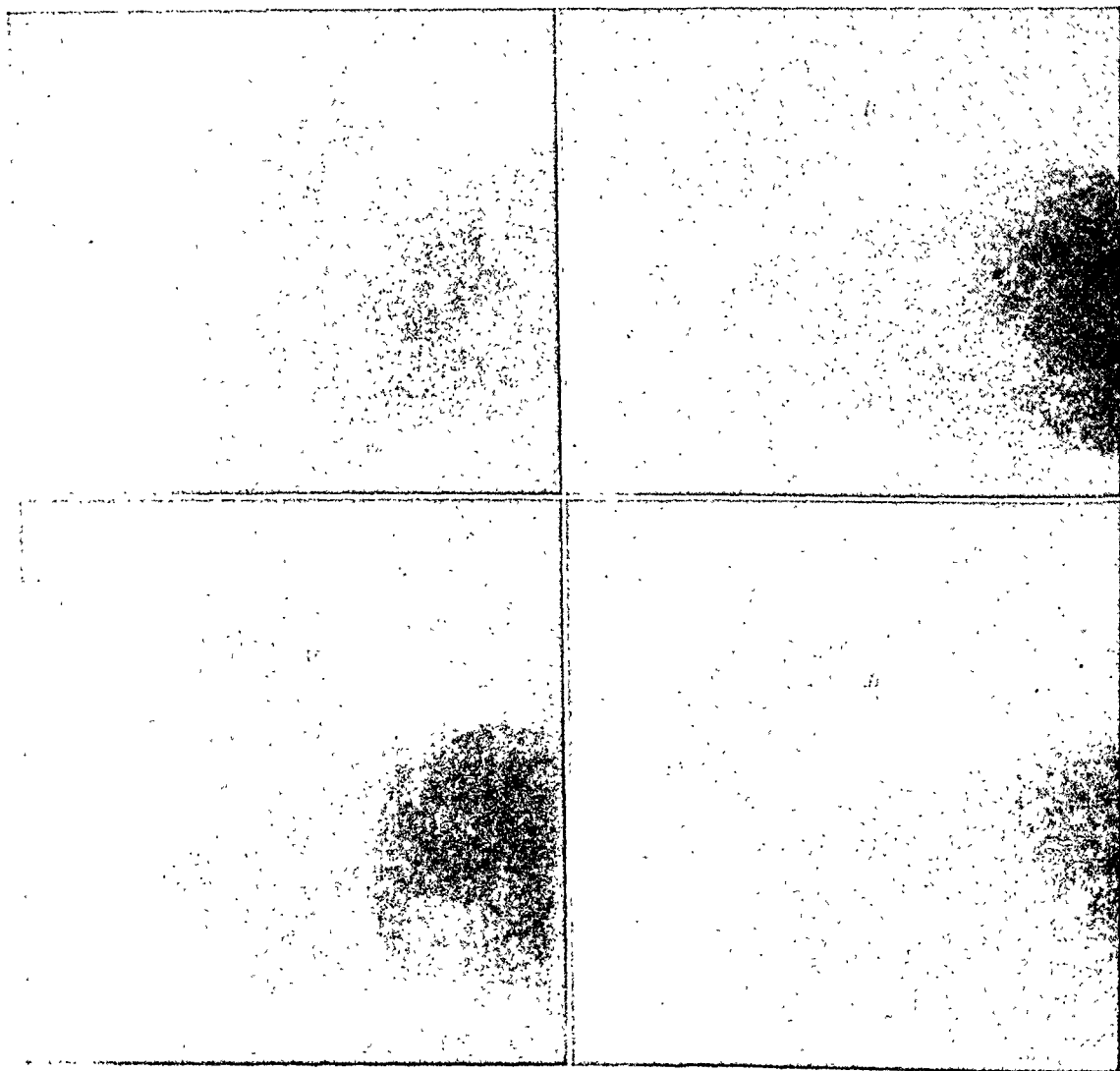


FIG. 3. Series III. Number 1.

exists without symptoms. Spontaneous perforation or hemorrhage is frequently the first evidence of ulcer disease. In view of these facts, well known to the medical profession, and especially, in view of the excellent power of the gastric mucous membrane to regenerate (as proved by the results of present day gastric surgery) it becomes extremely hazardous to say that trauma can produce a chronic peptic ulcer.

Liniger and Molineux²² have specified certain postulates that must be satisfied before trauma can be held as the cause of ulcer.

- Postulate 1. Proof of the absence of gastric disease prior to the accident.
2. The trauma must be severe and localized to the epigastric region.
 3. The immediate onset of symptoms.
 4. The continuation of symptoms and signs that point to gastric ulcer.

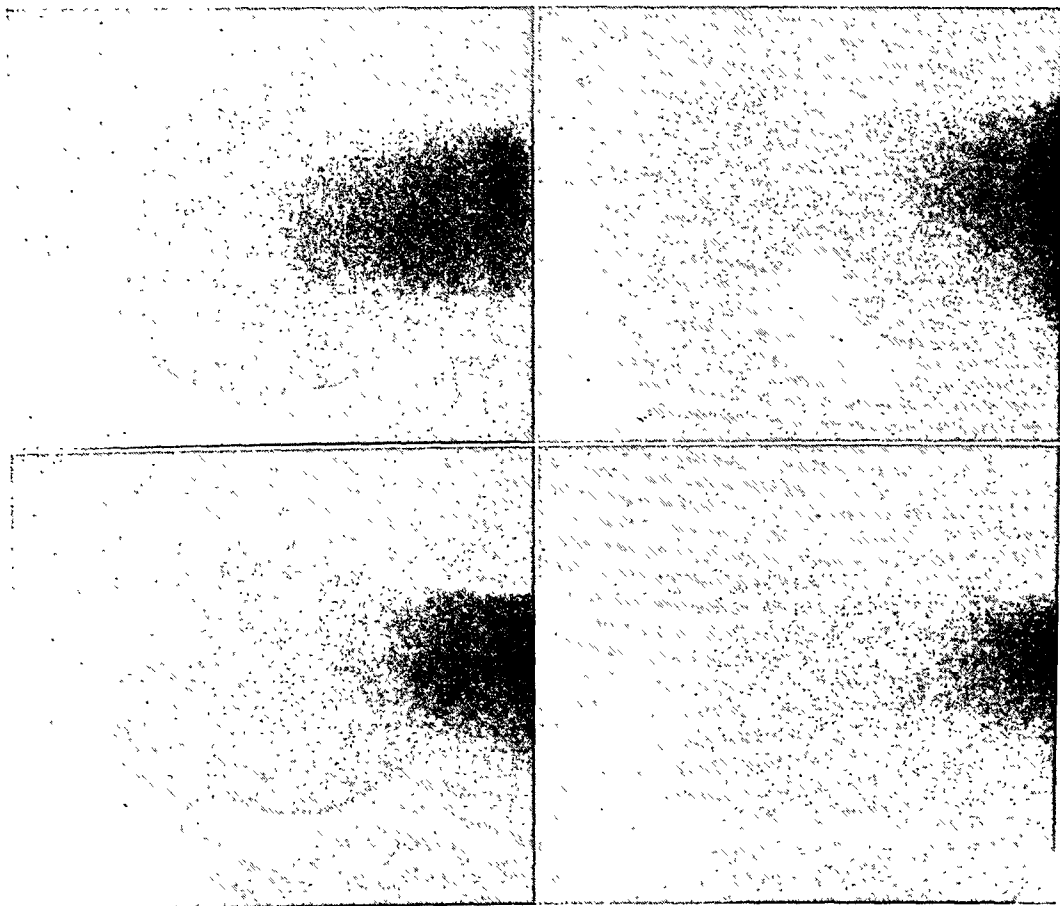


FIG. 4. Series IV. Number 1.

The proof of the absence of gastric disease prior to the accident must be furnished by the injured person, and quite naturally that is frequently impossible. If an individual has no symptoms he assumes that he is well and does not consult a physician. Even if perchance that ideal condition prevails in which every individual does have a health examination each year, fluoroscopic and x-ray studies of the stomach would have to be done to prove the integrity of the gastric mucous membrane. Postulate 1, namely "proof of absence of gastric disease" can only be obtained by laboratory procedures. We all have learned that the presence or absence of gastric symptoms is no true index of gastric disease. Under a strict interpreta-

tion of the postulates advanced by the above named authors few cases would be held compensable.

In the literature one finds a moderate number of case reports in which external trauma was held to be the responsible agent for the production of a chronic ulcer of the stomach. Recently Ramond and Chêne²³ reported two such cases. In their cases, however, as well as in the case reported by Gerendasy,²⁴ we must assume that the absence of digestive symptoms prior to the accident is synonymous with the absence of gastro-duodenal disease.

Griffiths²⁵ reports a case of trauma as the cause of chronic gastric ulcer confirmed by surgery. A laborer, aged 58, was struck in the epigastrium by the handle of a spade while unloading brick dust. He was transferred immediately to the hospital where he collapsed and vomited blood-stained material. An exploratory laparotomy done six weeks after the injury showed the presence of an ulcer a quarter of an inch in diameter, on the anterior aspect of the stomach near the pylorus and lesser curvature. There were no adhesions to the stomach and the wall of the ulcer was slightly indurated. Difficulty with the anesthetic and cessation of breathing prevented surgical intervention. About six weeks later the patient had a recurrence of hematemesis and a month later a second operation was performed. The stomach was now found to have several adhesions to the abdominal wall and to the liver. The ulcer was slightly larger than when first seen and the contiguous gastric wall was indurated over a greater area. Posterior gastro-jejunostomy was performed and the vestibule of the stomach and pylorus excised. The patient made an uneventful recovery. Histological examination showed no evidence of malignancy. Griffiths goes on to state that the patient had suffered for a short period from indigestion four years prior to the accident. He further states: "When first examined I thought his condition was in all probability due to hemorrhage from a chronic gastric ulcer which in some way had been injured at the time of the accident, but in view of the fact that at the first operation, six weeks after the original accident, there were no adhesions in the region of the ulcer and there was little induration of the surrounding tissue, whereas at the second operation three months later, there were several adhesions in the neighborhood of the ulcer which had increased in size and its margins become much more indurated, it seems to me likely that when first seen the ulcer was in a comparatively acute stage and in all probability started at or about the time of the accident."

In view of the history of digestive disturbances four years prior to the accident, it is possible that trauma acted as a revealing cause of an existing disease. Aggravation of preëxisting disease cannot be excluded.

In the older literature there are several reports in which the diagnosis of chronic peptic ulcer was made following trauma. The most interesting case was that reported by Potain,²⁶ of which mention has already been made.

Kronlein²⁷ reported two cases in which he described duodenal ulcer as a result of trauma. In the first case described, a young man of 24 was

thrown from his horse, his abdomen striking the pommel. Within 24 hours he developed severe pain after meals. Vomiting set in four weeks later. Four months after the accident the patient first came under the observation of Krönlein. There was marked gastric dilatation and epigastric tenderness. At operation eight months after the accident a stenosing ulcer of the pylorus was found and a resection was undertaken but death followed. At autopsy an ulcer of the duodenum with stenosis of the lumen was found. In this author's second case a man, aged 48, was struck in the abdomen by the handle of a pitch fork and was operated upon approximately three months later because of marked vomiting and loss of weight. The pylorus was resected because of suspicion of carcinoma. The specimen showed a healing pyloric ulcer.

Stern⁴ reports the case of a 33 year old laborer who fell against a piece of machinery, striking himself forcibly in the upper abdomen. He vomited the day after his injury and five days after the accident the vomitus contained small amounts of blood. For a period of eight months thereafter he continued to complain of pain in the stomach region especially after eating solid foods. Epigastric tenderness persisted. The continuance of subjective symptoms was suggestive of chronic ulcer disease.

A 46 year old man, who had never had any digestive symptoms, was observed by Gross,¹³ immediately after having been kicked in the abdomen by a cow. Several hours later he vomited blood. This recurred the following day. Tenderness in the epigastrium was marked. Four days later the first evacuation was found to contain a great deal of blood. From the tenth to the twentieth day the stools were again bloody although the gastric symptoms had practically disappeared and the epigastric tenderness was very slight. Although most of the symptoms abated within three months, subsequent inquiry revealed the fact that later on he had frequent gastric disturbances associated with attacks of bloody vomiting.

In the case reported by Theim,²⁷ a 47 year old worker with a history of excellent health was kicked in the stomach by a cow. Severe pain in the abdomen followed shortly thereafter but gradually disappeared only to recur within a few days. On the eleventh day he had sudden nausea and severe bloody vomiting. This repeated itself frequently during the following few days and was accompanied by marked tenderness in the region of the stomach. After 10 months, tenderness on pressure in the region of the pylorus was still present. Palpation showed increased resistance in this area.

Levig²⁸ reports a case of a 40 year old sentinel who fell in such a manner that the butt of his gun hit him in the stomach. The impact was so strong that the handle of the gun was broken. Subsequently the patient had pain in the epigastrium which lasted for about eight days and was aggravated by the intake of food. There was no vomiting. Pain gradually disappeared but after a lapse of several months recurred and was associated with regurgitation, heartburn and distention. Later vomiting began, occurred five to six hours after meals, was said to be dark brown in color and had a

bitter taste. Approximately one year after the accident he was seen by the author, who obtained the history as outlined above. Further information revealed that the patient had recently fainted and that he was vomiting frequently, often with blood, and that there was increasing pain. Physical examination showed a pale, emaciated individual with exquisite tenderness in the pyloric area and the presence of epigastric hernia. The vomitus showed a weak HCl reaction and contained lactic acid, yeast and sarcinae. The patient's condition improved with rest in bed and dieto-therapy but there was occasional vomiting of a coffee-ground like substance. The vomitus and stool both contained blood. The possibility of carcinoma was considered in view of the presence of lactic acid and the coffee-ground vomitus. Operation was not performed. By observing his diet and with the institution of frequent gastric lavage, improvement was gradual and one year and a half later this author states that "the patient now looks healthy and has no further gastric difficulties."

P. Müller²⁹ reports a case in which a 45 year old male fell approximately nine feet from a ladder. He was found unconscious with blood on his beard and about a cupful of blood beside him. Upon regaining consciousness he complained of severe pain in the epigastric region. After several weeks' rest in bed, soft diet, etc., he recovered sufficiently to go back to light work. Shortly thereafter he began to have nausea and bloody vomiting. Since then there has been a recurrence of hematemesis approximately every two months for a period of five years. Five years after the injury he was admitted to a hospital complaining of dull pain in the upper abdomen. Pressure elicited tenderness especially in the left epigastric area. He had two attacks of bloody vomiting during his stay in the hospital. After 10 years it was reported that vomiting still continued every seven or eight weeks and was preceded by anorexia, nausea and bitter taste. Vomiting would relieve the symptoms. The epigastric area continued to be sensitive and the patient continued to live on a light diet.

These case reports, from a clinical point of view, were considered indicative of the possibility of a chronic peptic ulcer having been initiated by external trauma. In the absence of roentgen findings or surgical intervention it is difficult correctly to evaluate the rôle which trauma played as a factor in the production of these gastric symptoms.

AGGRAVATION OF ULCER DISEASE BY TRAUMA

There can be no difference of opinion as to the question of trauma aggravating a peptic ulcer known to exist. The changes that follow may be mild or severe depending upon the character of the blow and the extent of gastric injury. As evidence of the severity and duration of symptoms resulting from epigastric injury in an individual known to have duodenal ulcer the following case may be cited:

CASE V

A male adult of 52 was operated upon for a duodenal ulcer 17 years prior to his accident. A gastro-enterostomy had been performed and the patient lived in comfort until November 1931, when he was struck in the upper abdomen by an iron bucket. Immediately thereafter he developed severe pain and within 24 hours began to vomit. Vomiting persisted for a period of two weeks upon the intake of any fluid or food whatsoever. The vomitus was bitter in taste, greenish in color and occasionally blood streaked. I first saw the patient approximately one year after his accident, at which time he was still complaining of epigastric pain and was vomiting at least once a day. Roentgen-ray study on several occasions during the year, following the accident, showed a well functioning gastro-enterostomy and a constantly deformed and contracted duodenal bulb. The stomach was hyperactive and usually emptied within an hour. There was no evidence of an ulcer along the lesser curvature of the stomach nor was there any evidence of a gastro-jejunal ulcer. Physical examination in November 1932 (one year after the accident) was essentially negative except for evident under-nutrition and the presence of exquisite tenderness in the right epigastrium. During the past 13 months that this patient has been under my observation there have been periods of improvement lasting several weeks. The symptom complex of duodenal ulcer as described by Moynihan³⁰ was quite distinct but was less active during these periods of regression. Recent roentgen-ray studies continue to show a deformed bulb and on fluoroscopic examination a small stream of the barium is to be seen passing through the pylorus and into the duodenum. Pain 30 minutes to one hour after meals is still a prominent symptom and vomiting occurs when too much food is taken. Epigastric tenderness is still present.

Trauma in this case undoubtedly aggravated a healed duodenal ulcer and in addition disturbed the motor mechanism of the duodenal loops adjacent to the gastro-enterostomy, producing disturbances in the motility, responsible for the vomiting. This man had been free of all symptoms for a period of 17 years prior to his injury. External trauma in this case is distinctly responsible for the aggravation of a known preëxisting ulcer.

SYMPTOMS AND PROGRESS

The symptoms most frequently present are those associated with local injury. If the trauma is severe there may be general evidences of shock. Epigastric pain and tenderness are most frequently due to abdominal muscle injury. If gastric symptoms such as nausea, discomfort after meals and vomiting follow, then it is not uncommon to find pain and tenderness a pronounced feature long after the muscle injury has subsided. Vomiting is probably the most frequent complaint. The presence of blood in the vomitus or in the stool is indicative of mucosal injury. In practically all of the cases reported in the literature peptic ulcer following trauma occurred on the lesser curvature of the stomach. The danger of gastric injury following external trauma is greater when the stomach is full. This has been shown both by animal experimentation and clinical observation.

Hematemesis may occur either immediately or several weeks after injury and the severity of bleeding is in no way parallel to the extent of gastric trauma. In the opinion of Stern,⁴ the absence of hematemesis does not

speak against the presence of gastric injury. Occasionally the cause of a massive gastric hemorrhage cannot be found at postmortem examination. Even when gastric hemorrhage occurs after trauma, autopsy may fail to reveal the cause of hemorrhage. Weimann³¹ reports two cases of epigastric trauma followed by hematemesis which recurred at intervals for many years and at autopsy cause for the hemorrhage was not found.

From personal observation of the five cases reported above, symptoms such as distress after meals, with pain occurring from 10 minutes to two hours after the intake of food, persisted for many months after the accident. Epigastric tenderness and muscle spasm were frequently found and varied in intensity and duration. It was difficult to evaluate correctly the alleged symptoms because in each case the factor of compensation played a dominant rôle.

The onset of the digestive symptoms usually occurs immediately or very soon after the injury. It seems rather misleading to attempt to build a symptomatology upon the basis of assumed pathological changes. It is reasonable to state that a hemorrhagic infarct precedes hemorrhagic erosion and ulcer formation. This infarct may be due to local circulatory disturbance, thrombosis, embolism and vasoconstrictor influences as pointed out by Silberstein.³² These circulatory disturbances may be interpreted according to the neurogenic theory of von Bergmann,³³ as brought about either by spasm of the arterial wall, or by spasm of the muscular coats of the stomach preventing the venous outflow or causing a transitory occlusion of the arterial flow.

Admitting the possibility of a hemorrhagic infarct and circulatory disturbance in the stomach following trauma, the question that immediately arises is whether or not ulcer can be produced by secondary infection or by the destructive action of gastric juice. Without entering into a discussion of constitution in relation to disease it may logically be asked: Can the application of a strong blunt force to the epigastrium produce a peptic ulcer, in an individual who has an ulcer diathesis? In the report of 200 cases of peptic ulcer, Friedenwald³⁴ noted that there was a history of trauma to the abdomen in 2 per cent of this group. Mattisson,³⁵ in his report of 25 cases of traumatic ulcer, states that in his opinion 1.5 per cent of all peptic ulcers have some traumatic insult before the onset of symptoms. The onset of symptoms in all these individuals would seem to point more toward external trauma as revealing preëxisting disease rather than as the causative factor of such disease.

SUMMARY

Five cases have been reported in which trauma played an important part either in the production or aggravation of preëxisting ulcer disease. Three of these five cases were diagnosed as acute traumatic peptic ulcer on the basis of epigastric injury, the presence of blood in the vomitus or stool or

both, with roentgen findings strongly suggestive of the presence of ulcer. All three made a complete recovery as evidenced by cessation of subjective symptoms, absence of blood in the stool and return of the gastric contour to normal as proved by roentgen-ray study.

One patient who came under my observation four months after his injury had a definite duodenal ulcer. Roentgen examination done six weeks after his accident revealed the presence of a duodenal ulcer. He was under my observation for a period of 18 months, during which time there was a continuance of subjective complaints typical of duodenal ulcer associated with constant epigastric tenderness. Repeated roentgen-ray study showed a characteristic deformity of the duodenal bulb but at no time was there any evidence of stenosis.

In case 5, severe epigastric injury aggravated a preëxisting duodenal ulcer which had been dormant for 17 years. In this patient some of the symptoms may have been due to disturbance in function of an existing gastro-enterostomy. The predominant disturbances, however, were associated with duodenal ulcer activity.

A number of cases were reviewed and cited in which the diagnosis of traumatic ulcer was made clinically, in some cases confirmed by autopsy and in others by operation. Cases proved by autopsy invariably showed multiple ulcerations of the gastric mucous membrane. In many of the cases the diagnosis was based on clinical symptoms only, the roentgen-ray not yet having come into use as a diagnostic aid. In this group, as well as in the small group in which surgery confirmed the diagnosis of traumatic ulcer, it was assumed that the absence of gastric symptoms prior to the injury precluded previous gastric disease and spoke for a normal integrity of the gastric mucous membrane. Such an assumption is not correct, for at the autopsy table scars of healed ulcers have been found in individuals who had not given any history of gastric symptoms. Furthermore, we know that ulcer disease may exist for many years and the first sign of such disease may be perforation or hemorrhage. If trauma were a factor in the production of chronic peptic ulcer it would be reasonable to expect its frequent occurrence after gastric surgery. That this is not the case speaks for the excellent regenerative power of the gastric mucous membrane.

Experimentally produced ulcer in animals readily heals. No one has ever been able to produce a chronic ulcer in animals by external trauma. The natural tendency in injuries to the gastric mucosa is toward complete healing. This is further borne out by the absence of symptoms and the undoubtedly prompt healing when the gastric mucosa is irritated by the passing of one of the larger stomach tubes. Not infrequently one sees gastric mucous membrane in the gastric content after extractions. Apparently there is rapid healing of the denuded mucosa.

It is interesting to note that the majority of cases quoted are in the German literature and that in 1927 the German State Insurance Office³⁰ went on record as denying any relation between trauma and gastric ulcer.

CONCLUSIONS

1. Acute traumatic peptic ulcer may follow the application of a strong blunt force to the epigastrium. The tendency in these cases is toward complete healing.

2. External trauma as a factor in the pathogenesis of chronic peptic ulcer is still a debatable question. If we assume that the absence of gastric symptoms prior to the trauma indicates a normal gastro-duodenal tract, then we may say that chronic peptic ulcer may be caused by external injury. However, in view of accumulated experience we know that the absence of gastric symptoms does not necessarily mean absence of gastric disease. Gastro-duodenal ulcer may exist for years and produce no symptoms. It seems reasonable and logical to state that trauma does not produce chronic peptic ulcer but rather reveals preëxisting ulcer disease.

3. Preëxisting ulcer disease may be aggravated by external trauma. The resulting disability depends upon the severity of the trauma and the pathological changes initiated by the accident.

This subject has great medico-legal importance. It has never been conclusively proved that one single trauma can produce a chronic peptic ulcer. In order to prove that trauma can produce a chronic peptic ulcer there must be roentgen-ray evidence of a normal gastro-duodenal tract within a comparatively short time prior to the accident. If there then follows abdominal injury and subsequent roentgen-ray proof of an ulcer is obtained and such evidence persists, then we may justifiably state that trauma has produced a chronic peptic ulcer. Otherwise the assumption that a chronic peptic ulcer was produced by trauma is entirely speculative.

BIBLIOGRAPHY

1. COHN, B. B., and GERENDASY, J.: Traumatic ulcer of the duodenum and stomach, Jr. Am. Med. Assoc., 1933, c, 1653-1658.
2. EUSTERMANN, G. B., and MAYO, J. G.: Etiologic relation of trauma to peptic ulcer, Am. Gastro-Enterological Assoc., 1933.
3. REHN, D.: Die Verletzungen des Magens durch stumpfe Gewalt, Arch. f. klin. Chir., 1896, lili, 383-400.
4. STERN, R.: Über traumatische Entstehung innerer Krankheiten, 2d Ed., 1913, G. Fischer, Jena.
5. PETIT, C. A. M.: L'ulcère traumatique de l'estomac, Thèse, Paris, 1913.
6. DUBRAY, J.: Contusion de l'estomac: accidents immédiats et consécutifs, Arch. gén. de Méd., 1881, ii, 339-343.
7. LEHM, W.: Ulcus ventriculi traumaticum, Centralbl. f. klin. Med., 1886, viii, 81-83.
8. STRAUSS, M.: Traumatisches Magengeschwür, Deutsch. med. Wchnschr., 1910, xxxvi, 895.
9. STERN, R.: Über traumatische Entstehung innerer Krankheiten, unter besondern Berücksichtigung der Unfall-Begutachtung, 3d Ed., 1930, G. Fischer, Jena.
10. POUVILLON, A.: Bull. Soc. anat. de Paris, 1856, xxxi, 385.
11. KERN, A.: Über den Einfluss von Traumen auf die Entstehung des Magengeschwürs, Ztschr. f. klin. Med., 1887, xii, 592-596.
12. VACCÀ, L.: Sull'ulcera dello stomaco d'origine traumatica, Sperimentale, 1889, lxiv, 113.

13. GROSS, G.: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1902, Bd. 10, s. 713.
14. QUINCKE and DAETTWYLER: Correspondenzblatt f. Schweizer Aerzte, 1875, s. 101.
15. GRIFFINI and VASSALE: Über die Reproduktion der Magenschleimhaut, Ziegler's Beiträge, 188, Bd. 111.
16. MATTHES, M.: Untersuchungen über die Pathogenese des Ulcus rotundum ventriculi und über den Einfluss von Verdauungsenzym auf lebendes und todes Gewebe, Beitr. z. path. Anat. u. z. allg. Path., 1893, xiii, 309-364.
17. FERTIG: Über Ulcus ventriculi traumaticum, München. med. Wchnschr., 1905, lii, 1781.
18. HAUSBRANDT, F.: Über traumatische Magengeschwüre, Wien. klin. Wchnschr., 1932, xlv, 681-684.
19. GRUBER, G. B.: Zur Frage über das Zustandekommen des peptischen Magen- und Duodenalgeschwürs, Deutsch. Arch. f. klin. Med., 1913, cx, 481-500.
20. LIBMAN, E.: Observations on sensitiveness to pain, Trans. Assoc. Am. Phys., 1926, xli, 305-308.
21. CROHN, B. B.: Pain sensibility; variable human factor, Am. Jr. Surg., 1929, vii, 474-479.
22. LINIGER, H., and MOLINEUS, G.: Der Unfallmann, 2d Ed., 1930, J. A. Barth, Leipzig. Quoted by KESSLER, H. H.: Accidental injuries, 1931, Lea and Febiger, Philadelphia.
23. RAMOND, F., and CHÊNE, P.: L'ulcère chronique de l'estomac d'origine traumatique, Presse méd., 1932, xl, 549-550.
24. GERENDASY, J.: Quoted by CROHN and GERENDASY.¹
25. GRIFFITHS, H. E.: Trauma and gastric ulcer, Lancet, 1922, ii, 329-330.
26. KRÖNLEIN: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1898-1899, iv, 493.
27. THEIM: Handbuch der Unfallkrankungen, 1909, Bd. 11, Tl. 11, s. 434-463.
28. LEVIG, W.: Inaugural dissertation, Kiel 1898. Quoted by STERN.⁹
29. MÜLLER, P.: Ulcus ventriculi et duodeni traumaticum, Inaug. Diss. Breslau, 1894.
30. MOYNIHAN, B. G. A.: Observations on gastric and duodenal ulcers, Practitioner, 1932, cxxix, 4-17. Prognosis of gastric and duodenal ulcer, British Med. Jr., 1932, i, 1-3.
31. WEIMANN: Zwei dunkle Fälle von Blutbrechen, nach Heben schwerer Lasten entstanden, Monatschr. f. Unfalld., 1900, vii, 69-75.
32. SILBERSTEIN, A.: Zur Genese des traumatischen Magengeschwürs, Med. Welt, 1927, i, 149-152.
33. VON BERGMANN, G.: Das spasmogene Ulcus pepticum, München. med. Wchnschr., 1913, lx, 169-174.
34. FRIEDENWALD, J.: In discussion on JORDAN, S. M., and KIEFER, E. D.: Factors influencing prognosis in medical treatment of duodenal ulcer, Am. Jr. Surg., 1932, xv, 472-482.
35. MATTISSON, K.: Gastric ulcer of traumatic origin, Hygeia, 1924, lxxxvi, 370-379.
36. German State Insurance Office; Quoted by KESSLER, H. H.: Accidental injuries, 1931, Lea and Febiger, Philadelphia.

STUDIES OF HYPERSENSITIVENESS TO THE EMANATIONS OF THE CADDIS FLY (*TRICHOPTERA*).

V. A REPORT OF ITS DISTRIBUTION*

By S. J. PARLATO, P. J. LADUCA, *Buffalo, New York* and O. C. DURHAM,
Chicago, Illinois

ALTHOUGH the first studies of the caddis fly emanations were made in Buffalo and the Niagara frontier, it was soon realized that this allergen was not confined merely to this locality.¹ An effort, therefore, has been made to determine the extent of distribution of this fly. The stimulus to do this was supplied by the numerous inquiries which have been received from physicians throughout this country and Canada as to the presence of this fly in their respective communities. This report also includes studies of its distribution in various sites in Buffalo and nearby rural districts. Daily counts of its emanations have been recorded and charted, much like the familiar pollen counts which are annually made in many cities.

A five years' search for data has necessarily been confined to books and monographs on insect life. Entomologists both here and in Europe have made numerous contributions on the distribution, structure, various stages of development and life habits of the caddis fly. J. T. Lloyd² states that: "The *Trichoptera* occur in all parts of the earth where any insect life can exist but their greatest abundance is reached in the northern temperate zone. All known caddis worms inhabit fresh water except a single species from New Zealand that lives in the ocean and a well known terrestrial species of Europe that lives in the moss of tree trunks." Such eminent entomologists as Klapalek,³ Struck⁴ and Ulmer⁵ who identified over 50 species of caddis flies, have reported that this excitant of asthma and hay fever has a wide distribution in Europe.

This fly flourishes in North America because the continent is covered with numerous lakes, rivers and ponds. Cornelius Betten,⁶ an acknowledged American authority on the caddis fly, states in the introduction of his forthcoming bulletin: "The total number of genera reported for the North American continent, including also Greenland and the West Indies, is 123 and the number of species, as listed in this report, 568. Of these species 261 are from the United States and Canada east of the Mississippi River and 271 from the western part of these countries, and from Greenland, Central America and the West Indies. Thirty-six additional species have so far been listed as common to the areas east and west of the Mississippi River but that number will doubtless be very greatly increased as further studies are made."

Vorhies⁷ writes that about 100 species of caddis flies were found within

* Received for publication March 2, 1934.

a radius of 30 miles from Madison, Wisconsin. He is of the opinion that they are found throughout that state. He also quoted Ulmer to the effect that this fly is seen abundantly in Minnesota, Illinois, Michigan and Canada.

Field studies have been made by us along the American shore of Lake Erie, visiting such large cities as Cleveland and Toledo. Great numbers of caddis flies were seen, particularly at the many summer resorts which dot the lake shore between these two cities. A trip about the City of Toledo was undertaken with Dr. Karl D. Figley who had previously stated that the caddis fly was not seen there.⁸ The visit revealed to him the presence of collections of flies about the street electric lights, around the lights of factories as well as homes and, what was particularly interesting, they were also found in places where he had usually seen mayflies which he has reported as excitants of asthma and hay fever. He concluded that the caddis flies were numerous enough as to constitute a fairly common but heretofore overlooked cause of allergic symptoms.

Studying the New York State fauna, Sibley⁹ found 80 species of the caddis fly. The residents of the Niagara frontier have long been familiar with this fly. The daily newspapers of both the Canadian and American cities annually publish stories, usually humorous, arising from the observation of the exceedingly great numbers of these flies during the summer months. Several field trips have revealed that this fly is found in abundance on the American shore of Lake Ontario and along a number of little rivers which empty into it. The Adirondack and Catskill Mountains with their numerous lakes and rivers, the Finger Lakes and Lake Chautauqua constitute an extensive habitat for this fly. Since these places are much favored as summer resorts, hypersensitiveness to the caddis fly should be considered in the treatment of patients who may be residing only temporarily in these places.

The emanations of the caddis fly consist of crescent-shaped hair and flat squamous epithelia which are shed by the two pairs of wings (figure 2). The hair is readily identified with the low power of the microscope. By exposing to the air an ordinary glass slide which has been smeared with vaseline or oil, the presence or absence of these emanations can be determined by microscopic examination without the use of any staining material. (Figure 3.) Along with his pollen counts, one of us (O. C. D.) has reported the presence of these fly emanations in the air of the following cities: Buffalo, Cleveland, Toledo, North Chicago, Chicago, Milwaukee and Port Arthur, Canada (figure 4). As time permits, it is expected that he will report on the presence of these emanations in other well known cities.

Our next step was to determine the extent of its distribution in various sites in the City of Buffalo and its suburbs. Twenty-four hour exposures of oil-smeared glass slides were made at several parks, hospitals, residences, hotels and downtown office buildings. (It should be stated here that practically all of the principal business section of this city is situated within one and a half miles of Lake Erie and the Niagara River.) Caddis fly hairs

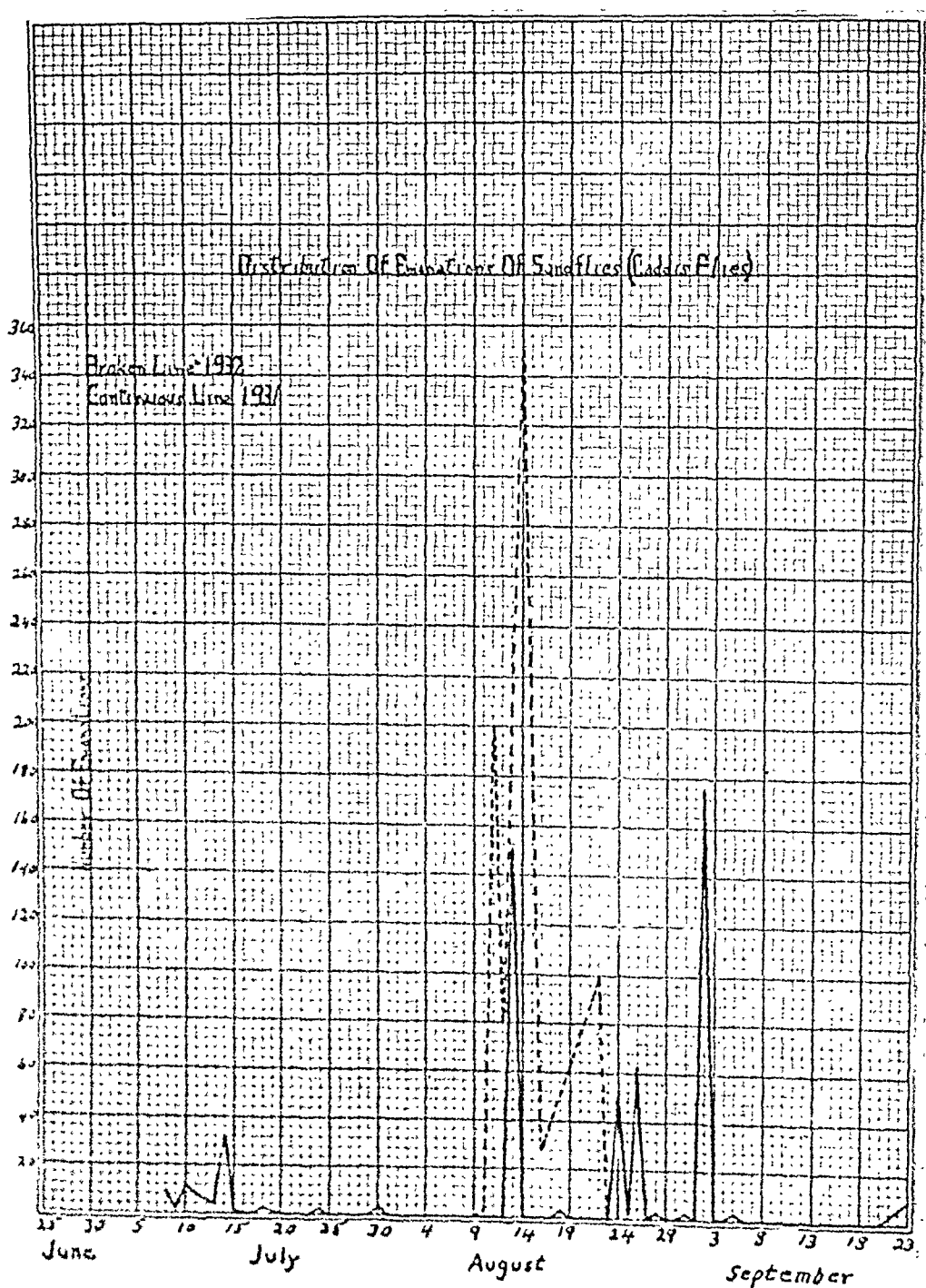


FIGURE 1.

were found in all these places. As one gets away from the lake or river, fewer of these emanations are encountered. None was found in the rural districts, which are more than six miles away from the river. However, directly opposite to Buffalo, there is a section of Canada which is used for summer resorts, bathing beaches and summer homes by Americans not only from Buffalo but from other cities of the United States. The greatest nuisance in these places is the caddis fly. Abundance of emanations has been found in the air throughout the summer months.



FIG. 2. Photomicrograph showing the characteristic structures of the fore and hind wings of the caddis fly. The denuded portions of the wings with irregular margins indicate the loss of hairs and scaly epithelia which are found in the air. Identification of these emanations on any exposed glass slide is made by the typically crescent-shaped hairs and not by the epithelia which lack definite shape or size and therefore do not permit ready recognition. ($\times 30$.)



FIG. 3. Photomicrograph of pollen plate exposed for 24 hours in the vicinity of Chicago, July 18, 1933. The presence of these typical hairs is definite proof that caddis larvae lived in Chicago. ($\times 300$)

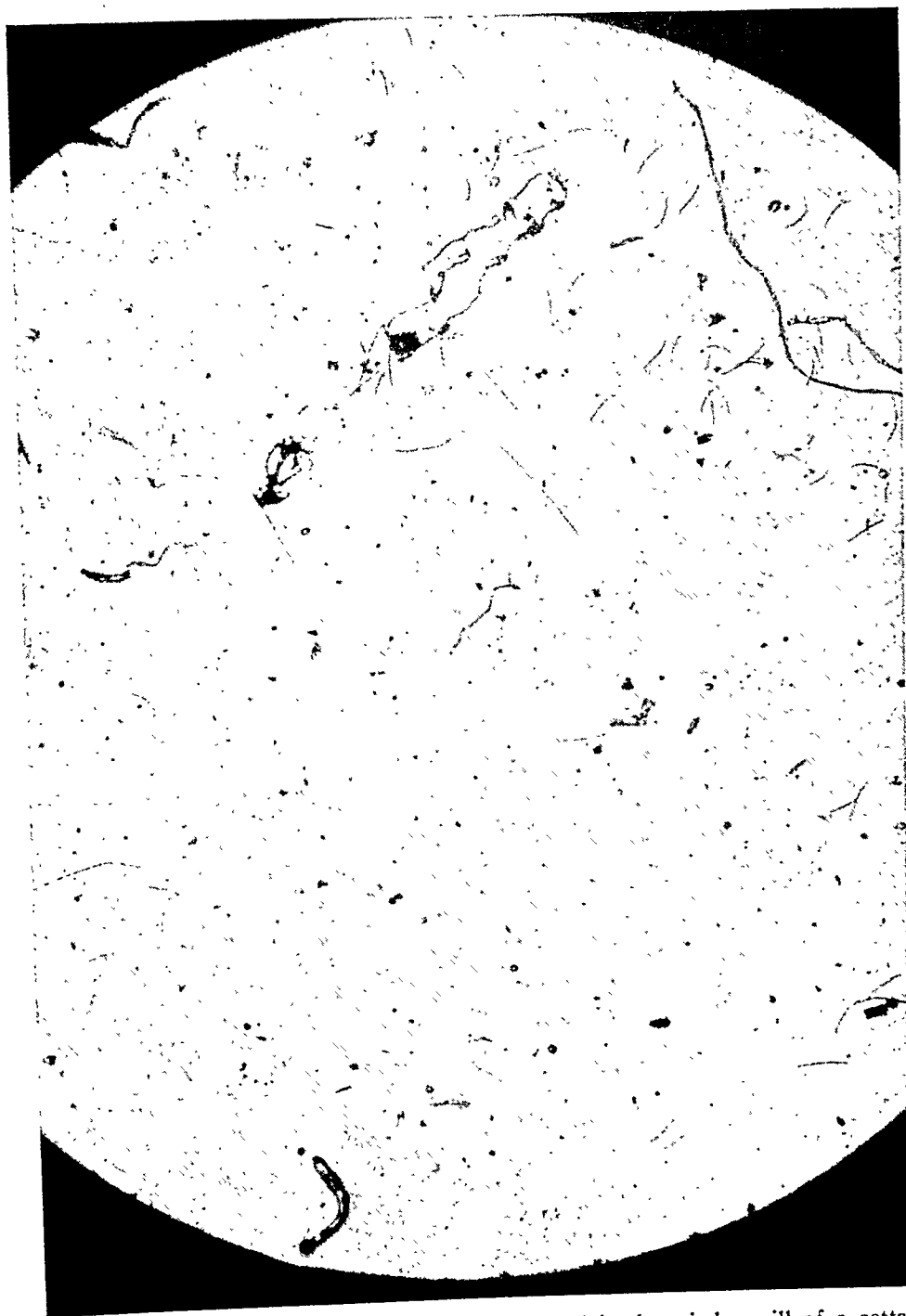


FIG. 4. Photomicrograph of dust which was found in the window sill of a cottage at Windmill Point, Ontario, Canada, about 8 miles from Buffalo. This is further evidence that caddis fly emanations are air-borne and cause allergic symptoms by inhalation. Incidentally, they constitute another and heretofore unrecognized component part of dusts. ($\times 30$.)

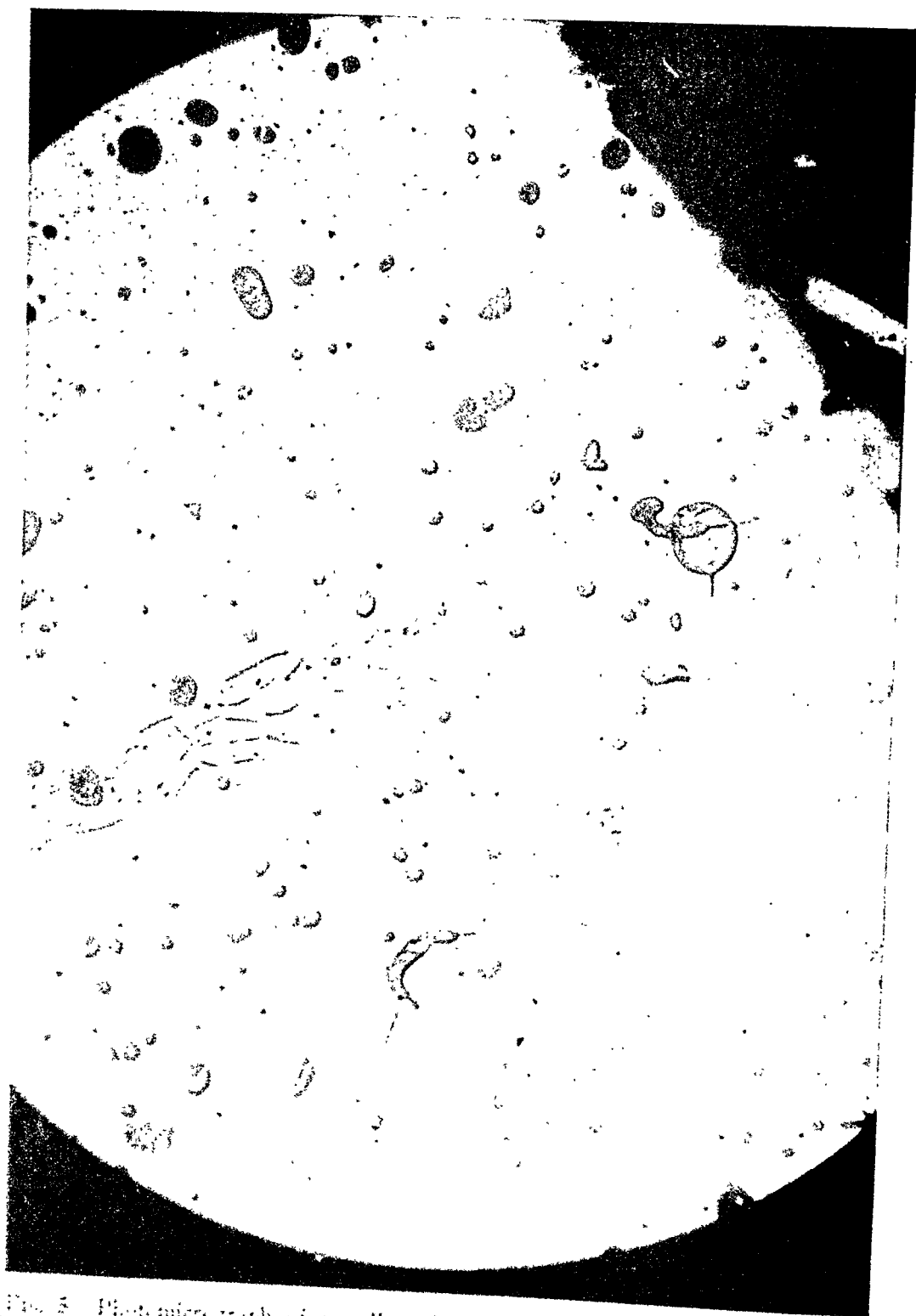


FIG. 5. Photomicrograph of a pollen plate exposed at Tampa, Florida, October 18, 1944. These are not caddy fly hair. Subsequent inquiry of the entomologist of the Agricultural Experimental Station of the University of Florida brought the information that these did not exist in Tampa. It is possible that these are fixed hairs which belonged to a caddy fly which was caught by the oil on the glass slide. ($\times 30$.)

To establish the daily relative intensity of distribution of this allergen, glass slides were placed on the tower of the United States Weather Bureau which is situated about 200 feet above the street level (figure 6). The plan

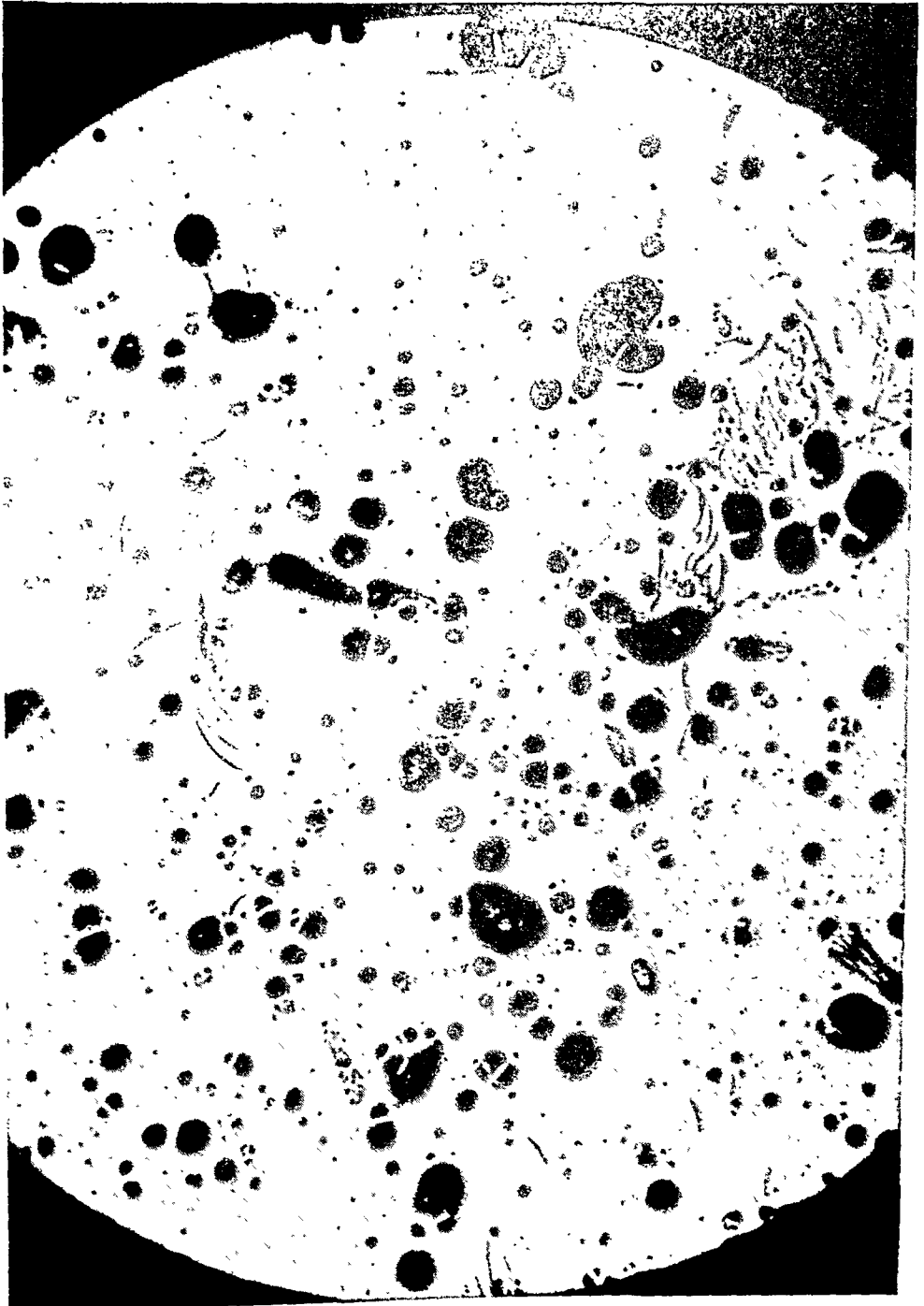


FIG. 6. Photomicrograph of glass slide which was exposed at the Buffalo Weather Bureau, September 2, 1931. Presence of caddis fly hair indicates that they are found abundantly even at a level of over 200 feet above the street. ($\times 60$.)

was to study these emanations in a manner similar to pollen counts. Daily counts were begun early in July 1931 although the first swarm of flies was seen on June 20. The study was continued through the summer until September 23, a few days after the end of the ragweed season. For the purpose of comparison, daily counts were also made during the month of August 1932. (See figure 1.) Incidentally, it has been observed that the 1932 fly season opened on June 15 and in 1933, June 8. This variation in the onset of its season is an important diagnostic point since, like the various pollens, it cannot be said that there is any set date for the initial appearance of these flies.

Further study of this graph shows wide variations in the atmospheric counts of these emanations. At best, this represents only a relative intensity of distribution. It must necessarily admit of some inaccuracy because these hair particles while counted like pollen grains probably do not readily adhere to the glass slides as they lack the sticky surface or spiculated margin which pollens possess. Furthermore, recent observations of the habits of this fly such as attraction to lights, tendency to fly near the ground, etc., lead us to believe that these counts are considerably lower than expected for the number of flies which are seen. This is especially true for the month of July. The high counts record the days not only when large numbers of flies were seen but also when their flight was aided by moderate winds. It was also noted that rain or a very cool spell, especially with northerly winds, caused a considerable reduction in their number, while hot sultry days favored their increase.

In this report, no emphasis is placed upon the number of species which have been seen in these different places. In the Buffalo area alone, several species have been identified, including the very small *T. microphilidae* to the common *T. limnophilidae* (figure 7). Skin and eye tests, which have been made with emanations of all these species, gave identical positive reactions. Structurally, the hairs are fundamentally the same for all the species. Moreover, extracts whether made from batches of separate species or several varieties together, gave similar positive tests. Immunologically, the *Trichoptera* give group reactions just like the various members of the grass family and like the *Lepidoptera* which include a large number of species of butterflies and moths.¹⁰

SUMMARY

Studies by leading entomologists show that the caddis fly is extensively found not only in the United States and Canada but also in Europe.

Our field studies have demonstrated that the caddis fly is not confined only to Buffalo and the Niagara frontier but is also seen along the Great Lakes and the several States and Canada which border on them. Its emanations therefore must be considered a possible factor in the etiology



FIG. 7. These flies were caught by passing an oil-smeared glass slide through a swarm of flies around a street corner light in Buffalo. The large fly is the *T. limnophilidae* which is the most common one. At the extreme right is the *T. microphilidae*. The other flies are midges (*Chironomidae*). Note the quantities of caddis fly hairs near their wings and throughout the slide. ($\times 6$.)

of the asthma and hay fever of people residing or on a vacation in this part of the country.

The presence of these emanations can be definitely established by the examination of exposed glass slides, the method being similar to that of pollen determinations for any community.

Examination of glass slide exposures have revealed that the hairs of this fly were found in various parks, hospitals, residences, hotels and downtown business office buildings in Buffalo. No emanations were seen in rural districts, six miles beyond the lake and Niagara River.

A study of the daily relative intensity of distribution of this allergen in Buffalo elicited wide variations from day to day during the summer months of 1931 and 1932. Like pollens, the amount of emanations which are found in the air is influenced by the ordinary meteorological factors such as temperature, humidity, velocity and direction of the wind.

A number of species of the caddis fly family have been identified, the *Limnophilidae* being the most common. Structurally, the hairs are the same for all the species. Immunologically, the *Trichoptera* give group reactions. In this respect, they act like moths and butterflies and the various members of the grass family.

REFERENCES

1. PARLATO, S. J.: Sand fly (caddis fly) as exciting cause of allergic coryza and asthma; its relative frequency, Jr. Allergy, 1930, iv, 307-312.
2. LLOYD, J. T.: North American larvae, Bull. of the Lloyd Library, No. 21, Entomological Series No. 1, 1921.
3. KLAPALEK, FR.: Metamorphose der Trichopteren, Arch. der Naturwissensch. Land-durchforschung von Böhmen 6, Band No. 5 and Band 7, No. 6.
4. STRUCK, R.: Neue und alte Trichopteren-Larven-gehäuse, Illus. Ztschr. Ent., Bd. 4, Nos. 8, 10, 13, 17, 19, 21, 22.
5. ULMER, G.: Die Trichopteren-Literatur von 1903 (resp. 1907), bis Ende 1909, Ztschr. f. wissenschaftl. Insektenbiologie, 1911 and 1912.
6. Personal communication.
7. VORHIES, C. T.: Trans. Wisconsin Acad. of Science, Vol. 16, 1909, page 647.
8. Personal correspondence.
9. SIBLEY, C. K.: Studies on *Trichoptera*, Bull. of the Lloyd Library, Cincinnati, Ohio, No. 27, Entomological Series No. 5, 1926.
10. PARLATO, S. J.: Emanations of flies as exciting causes of allergic coryza and asthma; study of atopic reagins of caddis fly, butterfly and moth, Jr. Allergy, 1932, iii, 459-468.

A CASE OF PERSISTENT LYMPHEDEMA INVOLVING THE LEFT ARM, LEFT FACE, AND LEFT THORAX *

By RAMSDELL GURNEY, M.D., and FRANKLYN HUBER, M.D.,
Buffalo, New York

THIS case is presented because of the paucity of reports on persistent lymphedema in the locations present in this patient.

CASE REPORT

On May 17, 1933, a white, unmarried, 16 year old American girl came to the Out-Patient Department of the Buffalo General Hospital for treatment of persistent, painless swelling of the left arm and left side of the face. According to the girl's mother, the child was taken to a doctor at the age of six weeks for an infection in her left eye. At that time the doctor called attention to the enlargement of the left arm and left face which until then the mother had not noticed. From that time on the arm and face have been persistently and markedly swollen. At the age of 13 months, the left hand became "infected" and since then, approximately twice a year, there have been infections of varying severity, involving the hand alone or hand and arm; occasionally the face is involved. The doctor who observed these infections is unfortunately deceased so a more exact description cannot be given. At the age of 10, the patient was seen in another hospital for a similar infection, and a diagnosis of "weeping eczema" was made. Since she has been under our observation she has had no skin lesion other than a red, elevated, non-tender area, 2.5 cm. by 1.5 cm., on the radial side of the first phalanx of the left index finger. This broke down in the center and healed in two days without any discharge; consequently, no culture was possible.

Both the mother and the patient report a slight improvement, especially of the facial swelling in the intermenstrual period, with the swelling most prominent just preceding and during the actual flow. This was borne out by careful and frequent measurements, the largest variation at any one time being 4 cm. in the elbow region. Catamenia started at 14 years of age, lasts four to five days, and occurs every 28 days with no irregularity but is accompanied by severe cramps on the first day. There has never been any pain in the arm or face and the only symptoms are those of tenseness and heaviness.

The mother is 40 years old and well. The father is living elsewhere and cannot be found for questioning. However, the patient's mother was acquainted with her husband's mother and father, and she remembers both of her own grandparents and parents in whom, and also in her five brothers and one sister, there was no swelling of any of the extremities or face. Her only other child, a boy, aged 15 years, is living and well. The patient's birth was easy and without instruments; weight 10½ pounds. She was nursed by her mother for three months and walked at nine months. During the teething period she had convulsions, the exact nature of which was undetermined. In early childhood she had measles, mumps, whooping cough, chicken-pox, pneumonia and tonsillitis. The tonsils and adenoids were removed at the age of nine years. For the past five years the patient has been well except for occasional gastric distress not related to meals.

* Received for publication March 2, 1934.

From The Service of Clayton W. Greene, M.D., Buffalo General Hospital, and the School of Medicine, University of Buffalo.

On physical examination the patient is 64.5" tall and weighs 125 pounds (56.8 kg.); temperature 98.6°; pulse 80 and equal in both arms; blood pressure, left 100-110/68-72, right 100-110/70-80. She is rather pale. Her behavior and conversation indicate normal intelligence. Her face is distorted by a smooth swelling of the left cheek which also involves the upper lid and ear. The forehead and scalp are not involved in this swelling, nor are the tongue and pharynx. The left ear is scaly and slightly thickened. There is no papilledema and the fundi appear normal. The skin over the left thorax, posteriorly and anteriorly, seems slightly thickened to the touch, but no pitting edema or dilated veins are present. Actual measurements with a caliper show the left chest to be 18 cm. and the right chest 15.2 cm. thick. The left breast is definitely larger than the right but not enough so as to be considered abnormal. The



FIGURE 1.

left upper extremity is greatly swollen—the hand and forearm more so than the upper arm. The skin is pale, smooth and pits on firm pressure. The depression, after pressure, pales and the indentation persists for some minutes. Both arms are the same length by measurement. All the other extremities are normal. No enlarged lymph nodes are palpable. The spleen is not felt. The rest of the physical examination is irrelevant.

The laboratory findings were as follows: r.b.c. 4,050,000; hemoglobin 81.6 per cent (13.8 gm.); w.b.c. 5,200, with polymorphonuclears 60 per cent, lymphocytes 40 per cent. Urine examination was negative. The Kahn test was negative. Serum albumin 4.63 gm. and serum globulin 2.70 gm. in 100 c.c. N. P. N. 28 mg. per 100 c.c. Blood calcium 10.5 mg. per 100 c.c. Blood chlorides 454 mg. per 100 c.c. Oxygen content of the venous blood taken without a tourniquet and after both arms were at rest for 15 minutes was: left 16.6 volumes per cent, right 16.5 volumes per cent. McCloy-McClure saline absorption test showed 60 minutes for absorption on the right arm, 15 minutes on the left arm. Both chests, anterior and posterior, had equal absorption times. The basal metabolic rate was minus 12.2.

Radiographic examination of the upper left extremity did not show any pathologic lesions affecting either the size, shape or character of the bone density. It showed a very much enlarged shadow of the left arm as compared with the right one. The space between the skin and the muscle was very much widened and the density of the muscular structure was increased over that of the opposite arm. The hypodermal

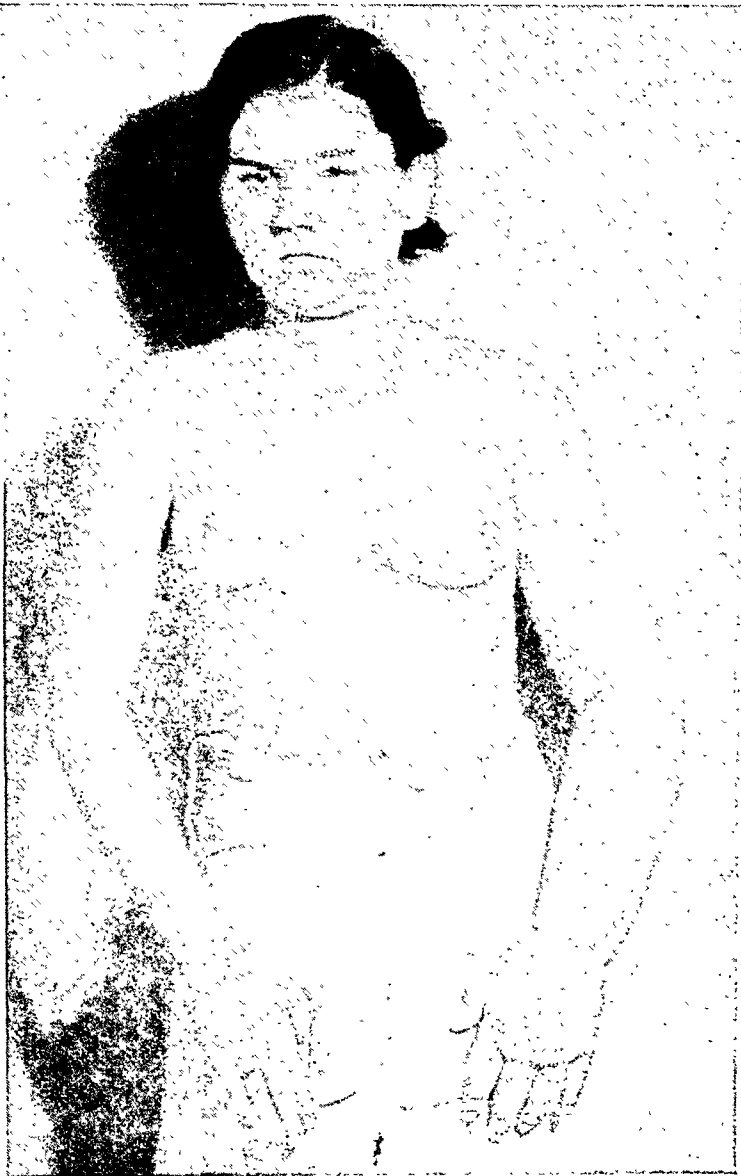


FIGURE 2.

space showed a net-work of fine lace-like shadows which apparently was a thickening of the subcutaneous tissues from the long-standing lymphedema. This net-work is apparently characteristic in the roentgen-ray of the trabeculation of an elephantoid state. Radiographic examination of the chest made in the lateral, oblique and posterior-anterior positions shows slightly increased density in the left chest which may be increased density of the soft tissue overlying this portion of the chest in the

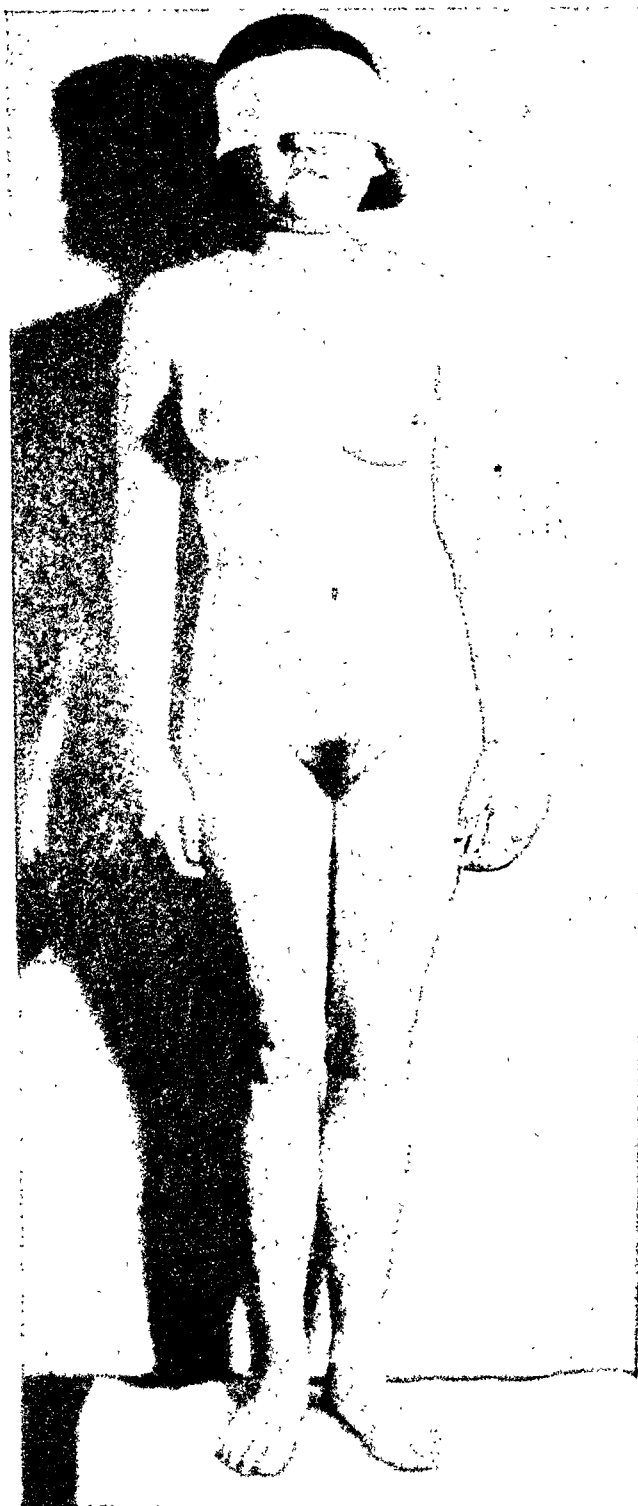


FIGURE 3.

There is no thickening of the pleural sac. The apices are quite clear. The diaphragm is regular. The heart shadow is not enlarged. The hilic shadows are normal size, with one or two small calcareous deposits especially in the left hilus. There is no evidence of growth or tumor or any density which may have influence upon the working of the arm. The transverse processes of the seventh cervical vertebra are a trifle long but there is no evidence of a cervical rib. (Dr. E. C. Koenig.)

DISCUSSION

It seems reasonable to assume that this is a case of congenital obstruction to the lymphatic drainage of the left side of the face, left arm and the left thorax. The absence of history of swelling in any member of the family and the fact that the legs are not involved, takes this case out of the group described by Milroy¹ and Hope and French.² The absence of cyanosis and dilated veins, and the normal oxygen content of the venous blood rule out the possibility of venous obstruction as the cause of the edema. The persistence of the swelling and its presence since birth are inconsistent with angioneurotic or endocrine factors as the precipitating cause.³ The history is definite, certainly as pertaining to the arm, that no infection preceded the swelling. Since that time there have been repeated infections both of the hand, lower arm and face which, unfortunately, we have been unable to observe. Thus, there is doubtless an elephantoid state present at this time, which fact is borne out by the roentgen-ray findings.⁴ Presumably, the lesion is at the point where the left jugular, left subclavian, and left bronchomediastinal trunks enter the thoracic duct. It is not impossible for these three to join, just before their exit into the thoracic duct, in a common duct which might be involved in a congenital obstruction. Or again, the right lymphatic trunk might have undergone excessive growth during embryological development, thus giving a reversal of the usual findings and resulting in a left lymphatic duct draining the left side of the head, the upper left extremity and the left chest.⁵ With such a condition, a congenital stenosis of this duct would not seem out of the realm of possibility. Of course, any interpretation of the cause of the obstruction is only conjectural.

REFERENCES

1. MILROY, W. F.: An undescribed variety of hereditary edema, *New York Med. Jr.*, 1892, lvi, 505-508.
2. HOPE, W. B., and FRENCH, H.: Persistent hereditary edema of the legs with acute exacerbations: Milroy's disease, *Quart. Jr. Med.*, 1907-08, i, 312-330.
3. SLATMANN, A. F.: Ein Fall von Trophoedema chronicum faciei in seinen Beziehungen zu der Menstruation, *Zentralbl. f. Gynäk.*, 1927, li, 2279-2282.
4. REICHERT, F. L.: Recognition of elephantiasis and of elephantoid conditions by soft tissue roentgenograms, with report of experimental lymphedema, *Arch. Surg.*, 1930, xx, 543-568.
5. PIERSON, G. M.: *Human anatomy*, 6th ed., 1918, J. B. Lippincott, Philadelphia, p. 944.

SANGRE IMPURA IN MORA

A STUDY OF SYPHILIS AND CERTAIN OTHER DISEASES IN THE POPULATION OF MORA COUNTY, NEW MEXICO *

By WALTER CLARKE, M.A., M.B., L.R.C.P. (Edin.), F.A.C.P.,
New York, N. Y.

BACKGROUND

IN the north-central part of New Mexico, in a region of rare scenic beauty and filled with the legends of the purple sage, "bad men," cowboys and cattle kings, lies the village of Mora, county seat of Mora County, a Spanish-American community in a state 60 per cent Spanish-American. Mora, a town of about 1,000 inhabitants, is surrounded by low mountain ranges, in the narrow, fertile valleys of which are numerous hamlets consisting usually of a dozen or so families, a general store and post office, a school house, and sometimes a tiny Roman Catholic church. The picturesque, but often insanitary dwellings and other houses are built of adobe. Mora lies on a rough dirt highway 32 miles from Las Vegas and 75 miles from Taos. As the narrow roads branching off from the highway to the hamlets on either side are all but impassable to motor traffic, travel from the hamlets to the local metropolis of Mora is principally by wagon or on horseback. Indeed, the inhabitants travel on foot from place to place over the mountain trails more quickly than the motorist can go over the rough roads, obstructed as they often are by boulders, mountain streams and mud.

About 10,000 people live in Mora County, a territory approximately twice the area of Rhode Island. The mountainous western portion of the county is more thickly populated than the eastern mesa region. Just what portion of the inhabitants are Spanish is not known, but in the western part of Mora County nearly every family bears a Spanish name and most speak only Spanish, though many have been born in New Mexico and their forebears have been in the United States for several generations. Some are descendants of the earliest Spanish settlers antedating the English settlements on the Atlantic Coast. Great pride in their pioneer ancestry is felt by such families, and they not only resent being called "Mexicans," but they look with condescension upon the "Anglos" whose families have no such romantic history and who, in most cases, have but recently arrived in New Mexico. No secret is made by Mora inhabitants of the fact that many families have in their veins a strain of the blood of the oldest protectors of the southwest—the Indians.

As a very large proportion of the adult population of Mora County speaks Spanish only, an interpreter is necessary in order to communicate with them in English. Even the children in the public schools have dif-

* Reprinted by permission of February, 1916, P.M.

ficulties with English, so that the instructions given to them must be translated into Spanish if one wishes to be understood.

In his narrow valley, the typical Spanish-American inhabitant of today lives much as his ancestors did a hundred years ago. He has his little plot of land from which he harvests beans, pumpkins and chile. He has a cow or goat which supplies him with milk and cheese. He raises corn which he grinds himself or which he takes to a neighbor for milling. He has little or no money, especially now when there are few jobs to be had as shepherds or in the fruit orchards of Colorado. His food is, therefore, of the simplest: coffee, beans, pumpkins, corn, chile (both fresh and cured) and cheese. Little milk is drunk even by children except as a diluent for coffee.



FIG. 1. Women and children awaiting the opening of a diagnostic clinic.

The family water supply is drawn from an unprotected well, or from the ditch that trickles down the valley from hamlet to hamlet. A privy with open vault stands near the ditch. In the summer-time flies are everywhere, and especially after heavy rains the ditches and wells are often heavily polluted.

In Mora County large families are fashionable, or at least numerous pregnancies are customary although due to fetal and neonatal deaths many women who have had 10 or 12 pregnancies have but two or three living children. But sickness and death are viewed with considerable stoicism,—what Providence does is good, think the Spanish father and mother of Mora. Pain, illness and infirmities are borne with resignation and prayer, for medical care is not available to the majority of families. It may be

many miles to the doctor,—at this writing there is but one in the whole western part of the county. Usually there is no money to pay for medicine, even if, as is often the case, the doctor is willing to render his services gratuitously. Because of these economic factors, and due to the fatalistic attitude of the people, more than half of the illnesses ending fatally progress to the termination without the alleviating care of a physician.

ORGANIZATION

In New Mexico beyond the boundaries of Mora County are many Spanish communities essentially similar to those roughly sketched above. As the health and medical problems of the state are largely the problems of these people, the State Bureau of Public Health considered it necessary to a proper understanding of the needs of the state, that a medical study should be made in a typical Spanish-American county. Even a superficial consideration of the previously known facts, such as the high still-birth rate, suggested that syphilis might constitute an important factor in the health of these under-privileged communities. It was known that typhoid fever was prevalent, and it was suspected that Malta or undulant fever might occasionally occur. The aid of several state and national health agencies* was enlisted, and Mora County was selected as presenting a reasonably typical rural population. In this county an intensive study was made of syphilis and certain other diseases, the presence of which might be discovered by means of examinations of the blood. The blood tests were supplemented by a limited clinical examination of certain cases, as will be explained below.

The writer, representing the American Social Hygiene Association, undertook to make such a study in Mora County as part of a general study of the state health problems. In the general survey tuberculosis, syphilis and malnutrition were to be considered, while in Mora County syphilis was to be especially studied for the first time, so far as is known, in a Spanish-American population in the United States. Such a study, it was believed, would throw light upon the health problems of comparable Spanish-American communities throughout the southwestern part of the United States.

After the necessary technical services were provided, the first problem encountered was that of inducing an adequate and representative number of Mora County citizens to present themselves for examination. With the deplorable roads, the great distances, and the lack of conveyances, this was by no means a simple problem.

* The organizations cooperating in the New Mexico health survey are as follows: the State Department of Public Health Service, the Bureau of Indian Affairs, the New Mexico Bureau of Geology and Mineral Resources, the American Public Health Association, the National Tuberculosis Association, the American Social Hygiene Association, the National Society for the Prevention of Blindness, the New Mexico Tuberculosis Association and the New Mexico Social Hygiene Association.

In late October 1933, a competent public health nurse took up headquarters in Mora and, with the advice of the Director of the State Bureau of Public Health and of the local Health Officer, began the preliminary organization of the survey. Her procedure was to visit a selected hamlet and interview the school teacher, always a leading figure in the village, and persuade him or her to announce the holding of a free diagnostic clinic in the hamlet on a specified date. The children were asked to convey the message to their parents and friends. The announcement was repeated every day by the teacher, and the date written large and clear on the school blackboard. Next, the nurse visited the post office, a center for the distribution of all local news and gossip, made the arrangement clear to the postmaster and posted a notice in Spanish. Then she visited all the homes in the hamlet and asked everyone to come to the diagnostic clinic.

All of these discourses had to be carried on in Spanish, for which purpose as well as for others, a young man called "Gonzalo," was employed. The people were told that "a doctor from New York"—a rare curiosity in Mora County—would hold a clinic on a specified day and those who came could be examined for *sangre impura* (bad blood). *Sangre impura*, to Spanish-Americans, is not necessarily syphilis, but is a comprehensive term covering a wide variety of pathological conditions which, rightly or wrongly, are attributed to "bad blood."

The diagnostic clinic team consisted of the public health nurse, the Spanish lad, Gonzalo, and the writer. Each morning early the team set out from Mora in a dilapidated car, loaded with equipment, for a drive of five to fifteen miles over rough roads to the appointed village where the clinic, opening at 8:30 a.m., was conducted in the district school house or mission building.

SOME EXPERIENCES

The work of the nurse had been well done, and a large part of each village's population came for examination. Some came because of the opportunity to obtain free medical advice; many came out of curiosity to "see the doctor from New York." Most, however, came because the clinic provided the most exciting event which had occurred in these villages since "Billy the Kid" had frequented this region. Stern orders had frequently to be issued to keep the citizenry from crowding so closely about the table where blood specimens were being taken as to hamper the work, and it was often necessary to dispatch Gonzalo around the exterior of the school house to persuade the people to leave the narrow windows where they obstructed the meager light. In several villages a holiday was declared. In one a band of young men who had chosen seats where they could look through the windows and see the doctor and nurse at work, kept up a continuous serenade, singing to the accompaniment of guitars and banjoes. They followed the team to its second appointment, continuing

the music with even greater enjoyment. When a person showed pain or even fainted, as occasionally happened, the serenaders endeavored to key the music to an appropriate minor note. The clinics were evidently a great social success, and a good time was had by all, even by the "fainters" who suddenly found themselves the center of much sympathetic attention.

Unaccustomed as they were to the sight of blood in a syringe, a few men and women, and a few children, fainted, and such is the power of suggestion that when one individual suffered an attack of syncope, there were sure to be others. Great excitement was caused by several individuals who, under the nervous strain of unaccustomed medical attention, inadvertently had fits. The exclamations and prayers of the deeply impressed by-standers added to the commotion caused by the characteristic expressions of epileptic seizures.

The language difficulties were numerous and constant. One woman who appeared to be ill was asked to describe her trouble. She replied "Me feel weak." "Where do you feel weak?" asked the doctor. "In my head," she replied. Further questioning brought out the fact that she had a headache. A young man complained of pain. "Where is your pain?" he was asked. "In my valentine," he replied, placing his hand over his heart!

The apprehensions of many of these simple people at the prospect of a needle entering their veins were often amusing. A young woman, whom the nurse had previously asked to come for a blood test, arrived just as the equipment was being packed for the return to Mora. "Why do you come so late?" smilingly asked the nurse. "All day I have been in church praying for courage to come," replied the girl. "Well, now, you tell me if it hurts," said the nurse and, choosing a needle, she quickly and deftly drew a specimen of blood. "Did that hurt?" asked the nurse. "I hardly felt it," replied the girl. "Of course you hardly felt it," said the nurse. "Tell me, do you think it was your prayers or my skill that saved you from pain?" "Oh," said the girl, "it was my prayers."

To encourage children to submit to the blood test, a liberal supply of sweets was provided and each child who allowed a specimen to be taken was given a piece of candy. So successful was this procedure that a careful watch had to be kept to prevent would-be repeaters from effecting the exchange a second time.

Of the individuals from whom specimens were taken all but one were born in the United States and all but eighteen spoke Spanish and had Spanish names. In other words our group was almost exclusively native born Spanish-Americans.

HOW THE DIAGNOSTIC CLINICS WERE CONDUCTED

During a period of four weeks, 21 diagnostic clinics were held. The clinics were held in the district school houses except in five instances—three

were held in missions, and two in a convent. The applicants for examination were assembled in the school house and enrolled by the teacher. Having arranged the school desks and a table for our equipment and provided for rapid sterilization of needles and syringes by boiling over a kerosene stove, the nurse and the writer proceeded to take specimens first from adults and then from the school children. A total of 1,674 specimens was taken, and 1,646 were successfully transported to the laboratory and examined.

Arrangements had previously been made with the State Public Health Laboratory at Albuquerque for testing blood specimens for syphilis by the



FIG. 2. Mora men awaiting their turn in a diagnostic clinic.

Kahn and Wassermann tests,* for Malta (undulant) fever by an agglutination test and, in the case of Mora inhabitants, for typhoid fever by the Widal test. Each working day the specimens were taken 32 miles to Las Vegas and mailed to Albuquerque. The limited facilities of the laboratory made it necessary at first to restrict to about 100, the number of specimens sent each day. During the last few days of the study a larger number was sent.

* During the Mora County Survey, the State Public Health Laboratory employed the standard Kolmer two-tube Wassermann test which uses 0.1 c.c. serum in each tube. The antigen used was the C. and L. Wassermann antigen as supplied by Dr. Kolmer from the Research Institute of Cutaneous Medicine, Philadelphia. All the sera that were either Wassermann-positive or Kahn-positive were set up again using the four-tube Kolmer Wassermann test. In this 0.1, 0.05, and 0.025 c.c. were used with 0.1 in the control. Two tubes were used in the Kahn test with 0.05 and 0.0125 c.c. of antigen suspension respectively and 0.15 c.c. serum in each tube. The antigen was the standard Kahn antigen as supplied by the Digestive Ferment Company, Detroit.

While specimens were being taken, each person was asked a few simple questions, such as "Are you quite well?" and in the case of married females, "How many times have you been pregnant?" and "How many of your children are living?" Individuals who showed obvious signs of illness or infirmity were asked to wait to see the doctor. Others who, on their own initiative, requested an interview with the doctor, were invited to remain until all specimens had been collected. Those so selected—in all about 200 men, women, and children—were interviewed and given a brief clinical examination at the conclusion of the clinic. After obtaining, through an interpreter, a brief history of the principal complaint, a rapid clinical examination was made, giving especial attention to the circulatory system and the central nervous system afterwards. Simple suggestions were given to each person so examined as to what each might do to improve his or her health, or to remedy a defect.

It is of interest to consider the obvious medical conditions found among those examined clinically, bearing in mind the fact that this examination was necessarily superficial due to lack of time and because the only instruments available were a stethoscope and a pocket flash-light.

CLINICAL CONDITIONS FOUND

Among the most frequent conditions met with were impetigo contagiosa and scabies. Whole families were encountered with these conditions, in part a reflection of the unhygienic conditions under which they live. A few cases of psoriasis and one or two rare skin diseases were found. Chronic constipation was a frequent complaint, especially among women. Chronic gall-bladder disease was diagnosed in several cases. A few cases believed to have chronic duodenal ulcer were discovered. In one region, a valley north of Mora, was found a surprising number of large goiters, traceable, it is believed, to the water supply.

A considerable number of cases of tuberculosis was found, including two boys with kyphosis, three, tuberculous joints, one, tuberculous rib, and two cases in which a clinical diagnosis of pulmonary tuberculosis was made. In three of these cases of tuberculosis, syphilis was established as a complicating factor. One boy with tuberculous kyphosis and the two cases of pulmonary tuberculosis were found also to have positive Wassermann and Kahn tests. It is quite possible that the two cases in which a clinical diagnosis of active pulmonary tuberculosis was made and who were found later to have strongly positive Wassermann and Kahn blood reactions, did not, in fact, have tuberculosis. For it is by no means always easy, clinically, to distinguish between active tuberculosis and active syphilis. Certain general systemic manifestations of early syphilis, such as loss of appetite and of weight, paleness, weakness, raised temperature, headaches, chest pains, gastric disturbances and jaundice, are symptoms which resemble those of tuberculosis. In the secondary stage of syphilis, patients may suffer from

bronchitis and sore throat and nearly always present inguinal, cervical or other regional adenitis. Chronic syphilitic skin lesions and chronic syphilitic laryngitis are occasionally mistaken for tuberculosis. Pulmonary syphilis can cause alterations of lung tissues resembling those of tuberculosis. Where these two diseases co-exist in a patient the prognosis generally becomes more grave and treatment of syphilis must be carried on with great discrimination avoiding the iodides and using the arsenicals only after cautious treatment with the heavy metals and then, only in small doses. Since, with the facilities available, pulmonary tuberculosis could not be definitely ruled out in the two cases mentioned above, advice regarding treatment was based upon the assumption that both tuberculosis and syphilis were present.

Among other conditions found were: One case of blindness probably due to ophthalmia neonatorum, several cases of senile cataract, one of trachoma; one enormous hydrocele in a boy of seven years, one gonococcal arthritis, one acute gonococcal urethritis; one vaginitis in a girl of three years; four cases of chronic otitis media following measles or scarlet fever; one case believed to be carcinoma of the rectum, and one believed to be carcinoma of the cervix. An interesting case of purpura hemorrhagica, which had suffered an operation for appendicitis and gall-bladder disease, was examined and diagnosed.

One of the most interesting cases observed was that of a boy 16 years of age showing some features of the rare syndrome called osteopsathyrosis or Lobstein's disease. This lad had china-blue sclerotics and one iris was brown and one was blue. He was small and weak for his age and distinctly subnormal mentally. There was, however, no history of pathological fractures. Most subjects suffering from this disease, believed to arise from defective calcium metabolism due to endocrine dysfunction, die in infancy. The fact that our subject survived may indicate a minor degree of dysfunction. Osteopsathyrosis is sometimes associated with congenital syphilis but in this case the Wassermann and Kahn tests were negative and none of the numerous stigmata of congenital syphilis were present.

Malnutrition was apparent in a great many of the children seen. A consideration of the diet of these children,—the preponderance of beans, chile and pumpkins, the lack of fresh fruit, the failure to use milk even when the family possesses a cow or goat, accounts for a considerable part of the dietary deficiencies. The New Mexico State Agricultural College, as a part of the health survey of the state, is studying the diets prevalent in typical communities, and more careful observations and measurements than the writer was able to make are to be included in another part of the general survey of nutrition among the New Mexican children.

It is convenient to discuss the clinical manifestations and the epidemiology of Malta fever, typhoid fever, and syphilis, in connection with a consideration of the laboratory reports of blood tests for these conditions. For the purpose of this paper, Malta fever and typhoid fever will be discussed only

briefly, reserving for the consideration of syphilis the major part of the space available.

MALTA FEVER

Malta, or undulant, fever, is a specific infectious disease which has been reported with increasing frequency in the United States since its manifestations and methods for its recognition have become better known to the medical profession. It is characterized by a remittent or undulant type of pyrexia, a prolonged course associated with enlargement of the spleen, anemia, loss of weight and vitality, constipation and sweating. The onset

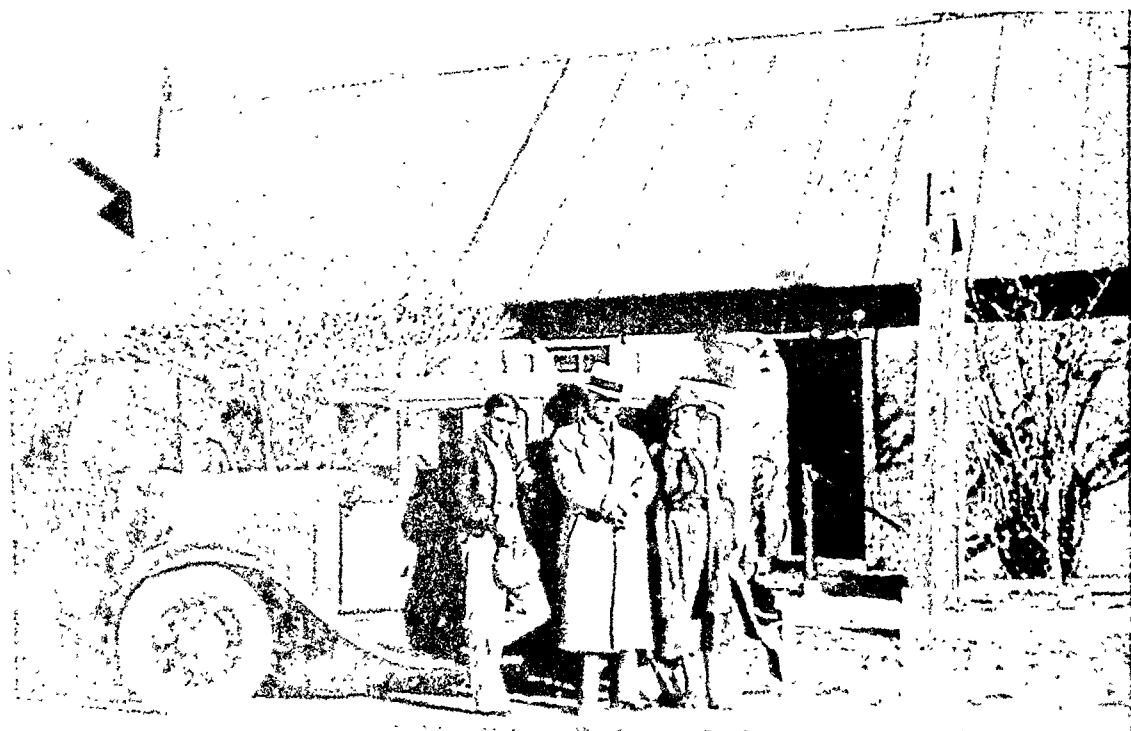


FIG. 3. The diagnostic clinic "team." Left to right, "Gonzalo," "the doctor from New York," and the public health nurse.

is insidious, the mortality low, and the convalescence prolonged. The *Brucella melitensis* is the causal organism. The sources of infection are cattle, goats, sheep, and swine, any or all of which may constitute a reservoir of infection. The disease is harbored in the genitalia of the male animal and in the uterus and mammary glands of the female animal. Among animals the disease is transmitted by sexual intercourse, so that it is in a sense an animal "venereal disease." In man, Malta fever is not believed to be communicable from person to person directly. The disease is transmitted to man by the ingestion of milk, by contact with the products of parturition of infected animals, and possibly by other contacts with infectious animal discharges. The portal of entry in humans is the gastrointestinal tract, the mucous membrane, and probably through abrasions of the skin. Hence it is clear that persons using unsterilized milk from in-

fectured cows, or goats, or acting as mid-wives to infected cows, she-goats, ewes or sows, are likely to be exposed to infection.

Our studies indicate that the Spanish-American families in Mora County commonly possess one or more cows or goats, and a pig or two. The milk of cows or goats is customarily used without boiling. One of the principal occupations of Spanish-Americans in this region is the care of great flocks of sheep. It might be anticipated, therefore, that if Malta fever is common among domestic animals, it might also be frequent among the inhabitants.

Agglutination tests for evidence of Malta fever were made on blood specimens from 1,621 inhabitants of Mora County in the course of this study, with the result that a total of 73 specimens, or 4.5 per cent of all, were positive. However, among the positives, only one, or 0.06 per cent of the total specimens, gave a reaction in dilutions as high as 1 in 80. It is believed, as pointed out by Mitchell and Humphreys,¹ that in man moderate degrees of positive reaction may be due to antibodies derived from ingested milk and may not indicate active infection or acquired immunity. Reimann² states that positive agglutination in dilutions of less than 1 in 80 is not significant evidence of infection. Twenty of the individuals giving a positive agglutination test for Malta fever were examined and questioned with the following results: none presented any symptoms or signs of Malta fever; none had any illness resembling Malta fever within the past two years; all used unboiled milk of cows or goats.

It is possible to draw only tentative conclusions from the findings briefly mentioned above. If Malta fever exists in this group, it is apparently of subclinical variety. The individuals who gave feeble positive reactions may have developed an active immunity, or small amounts of antibodies from ingested milk may have caused agglutination in low dilutions. In any case, it does not appear from this feature of our study that Malta fever is a serious medical or public health problem in Mora County. Nevertheless, all of the individuals examined were advised always to boil milk before using it, and to wash their hands carefully after caring for animals.

TYPHOID FEVER

Typhoid fever, on the other hand, is recognized as one of the most serious problems of Mora County, and indeed of the state. During 1933 there was a small outbreak of typhoid in the town of Mora and several cases occurred elsewhere in the county. The water supply of the town is drawn from wells, many of which are unprotected. The house fly is a great nuisance, especially during the warm season. As mentioned, there is no pasteurization of milk, nor is boiling of this article of diet customary. A part of the population has had anti-typhoid vaccination, but due to lack of funds this prophylactic measure has been curtailed during the past two years, so that with the lapse of time and diminution of the effectiveness of previous vaccination, a larger and larger number of people have become susceptible to this disease.

Since about 90 per cent of vaccinated individuals give a positive Widal test, specimens for the Widal test were taken, in the diagnostic clinic in the town of Mora, only from unvaccinated individuals, with the object of discovering carriers and cases of "walking typhoid." In Mora a total of 295 specimens was taken and of the total specimens tested, 34 or 11.5 per cent gave a positive Widal reaction. These positive specimens gave results classified by dilutions and by sex, as follows:

TABLE I

Dilutions	Number of positive reactions by sex	
	Male	Female
1-20.....	1	6
1-30.....	0	1
1-40.....	7	7
1-80.....	5	6
Over 1-80.....	0	1
Total.....	13	21

When we consider that these individuals were apparently healthy, that typhoid carriers may give a very weak Widal reaction, and that only unvaccinated individuals were tested, it seems probable that these 34 cases are at least potentially carriers of typhoid fever. Of the 34 cases giving a positive Widal, 12 were children in school, 12 were housewives, 3 were farmers, and 7 had other occupations. Rosenau² states that among carriers, females outnumber males 4 to 1. In our group, however, of the total of 155 females and 140 males examined, 13.5 per cent of the former and 9.3 per cent of the latter gave positive Widal reactions.

The most frequent focus of infection in typhoid carriers is in the gall-bladder and the bile ducts, the organism escaping in the feces. Therefore, the next step in finding the carriers of typhoid in Mora is to examine the feces of those who have positive Widal tests. As rapidly as possible this is being done, not, however, overlooking the need for better sanitation of the water and milk supply, and the necessity for better personal and home hygiene.

SYPHILIS

An impression exists in the southwest that syphilis is very prevalent among the Spanish-Americans. Indeed, physicians have told the writer that they believe it reaches proportions equal to that of syphilis among the American negroes. There were in New Mexico certain indications of a high syphilis prevalence rate such, for example, as a high still-birth rate, but it would appear the syphilis prevalence rate in Mora County is not very different from that which we believe to exist generally in the United States. The best statistical opinion obtainable places the general prevalence of syphilis in all ages, races and classes in the United States at about 5 per cent.

Serological tests of individuals in Mora County gave clear positive results in 5.8 per cent of the bloods of 1,646 men, women and children over 6 years of age. Of the total group, children from 6 to 11 were 2.5 per cent syphilitic, males 12 and over 6.9 per cent, and females 5.7 per cent.

The epidemiology of syphilis in Mora County presents no unique features. Although this district is far removed from great centers of population, syphilis finds its way into the village homes in the characteristic way. It is said that soldiers returning from the World War brought syphilis with them, and some of these same former soldiers were found, in the course of the study, to have late manifestations of syphilis. In normal times, particularly in the summer, many Mora men go to Colorado, or even to

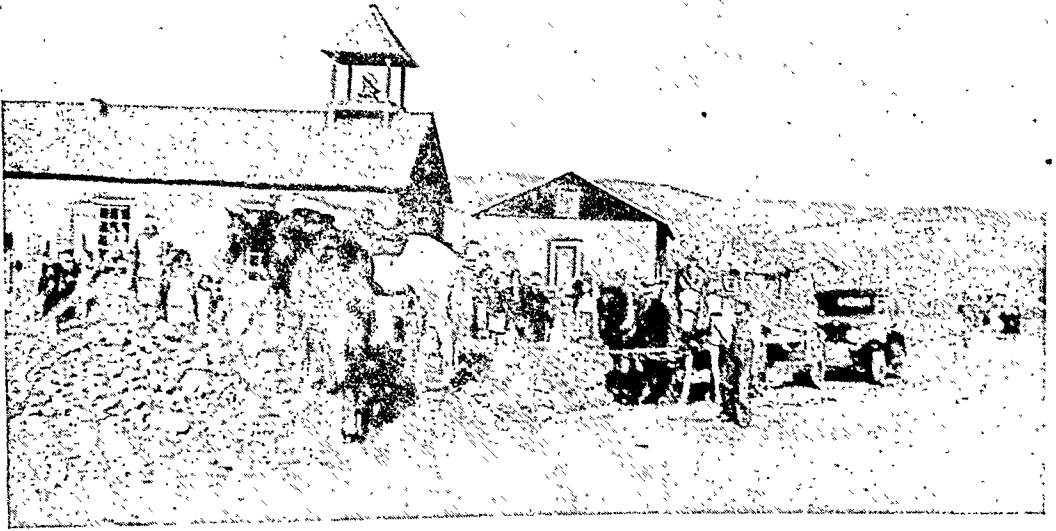


FIG. 4. One of the school houses in which a clinic was held; the methods of conveyance to the clinics.

Wyoming, to work as shepherds, or on the great ranches. Ordinarily they return to their families in Mora but first they may go on a spree in Cheyenne or Denver. Some cases of syphilis have been attributed to such workmen. However, not too much responsibility for the spread of syphilis is to be placed on the returning soldier and laborer, since there are well-known houses of prostitution in Las Vegas, and one even in the small town of Mora. To these brothels many of the men and boys of Mora turn for sexual gratification, and from them they carry syphilis into their homes. Wives and mothers are infected, and they in turn infect the unborn children, which accounts in part for the high still-birth rate previously mentioned. It is stated by Mora citizens that no unusual amount of sexual promiscuity, not properly called prostitution, exists among the inhabitants of Mora, but several cases of syphilis were found in which infection had occurred through intimate contact with a friend in the course of a temporary alliance.

One of the hopeful aspects of the problem among the Spanish-Americans is their frank and rational attitude toward syphilis. Surprisingly little stigma is attached to *sangre impura*. No embarrassment on the part of infected individuals was observed when they were questioned about the disease and the sources of infection. Prophylactic measures are practically unknown among them. Sanitary arrangements being what they are—no running water in homes, no modern toilet facilities—it is doubtful whether the prophylactic potentialities of soap and water used after exposure have been tried out by many Mora inhabitants. Insofar as syphilis and gonorrhea are regarded as serious diseases, they are looked upon as afflictions which an inscrutable fate holds in store for those who satisfy sexual hunger.

Various manifestations of syphilis were found among the individuals selected for clinical examinations in the diagnostic clinics. As previously mentioned, those chosen for this procedure were the obviously ill, and those who especially asked for medical advice. The most frequent syphilitic conditions found were ocular and cardio-vascular syphilis. Interstitial keratitis was found in four individuals. Other conditions of the eyes, believed to be manifestations of syphilis, were optic atrophy in a case of tabes dorsalis, and one case of syphilitic iritis. Aneurysm in a woman of about 30 years was of interest. She presented suprasternal pulsation, inequality of the pupils and of the radial pulses, and a dry cough. In this case the Wassermann and Kahn tests were positive. Aortic incompetence, probably of syphilitic origin, was diagnosed in one case and confirmed by positive serology. Several persons complaining of substernal pain and shortness of breath, and having a loud ringing second sound in the aortic area, were believed to have syphilitic aortitis. Ulceration of the leg in a woman of 33 years, who had had a diagnosis of syphilis and several injections of neoarsphenamine several years previously, was believed to be syphilitic. Nodular cutaneous syphilids, serpiginous in form, were observed in one patient who later showed a positive Wassermann and Kahn. No syphilitic chancres were found but, as it was impossible to strip every patient, this negative finding is not very significant.

It is always interesting to consider whether syphilis shows any special or predominant type of manifestation in a distinct racial or nationality group. Such a question has been raised with regard to the Spanish-American population of the southwest. Insofar as the population studied in Mora County is typical of the Spanish-Americans of New Mexico, one may say that syphilis is substantially similar in its predominant anatomical distribution to syphilis in the white part of the population of the United States generally, the only obvious differences being attributable to the general lack of medical care. But few of the infected individuals in Mora County had ever had a blood test before and only five gave a history of previous antisyphilitic treatment. Under such circumstances it was not surprising to find exceptionally advanced syphilitic lesions.

The 1,646 specimens of blood collected in the diagnostic clinics were submitted to two tests at the State Laboratory, namely, the Wassermann and the Kahn tests. For the purposes of this study specimens were classified as positive if the laboratory report indicated a strong (4 +) positive reaction in both tests, or a strong positive reaction to one test and a weak positive to the other, or where one test was a strong positive and the other test a negative. Weak positives to one test and negatives to the other were



FIG. 5. A mother and children who came to a diagnostic clinic in Mora County, N. M.

classified as doubtful, as were also weak positives in both tests. Fifteen specimens, or 0.9 per cent, were thus classified as doubtful, 95 or 5.8 per cent as positive, and 1,536 or 93.3 per cent as negative. It is to be remembered that a negative Wassermann or Kahn test does not rule out the possibility of syphilis.

In Mora County very little indeed is done for the prevention of congenital syphilis through the treatment of syphilis in pregnant women.

Prenatal medical care is not usually obtainable by women living in isolated villages, and even in the more accessible communities poverty prevents most women from consulting a doctor until the onset of labor. Hence, serological tests of pregnant women, the only practicable way of discovering 95 per cent of cases of syphilis in them, are not made. If syphilis is not discovered and treated, still-births and neonatal deaths are the frequent results. Some congenital syphilitic children survive in spite of intra-uterine infection and these show the characteristic stigmata of congenital syphilis. Of such cases a few were observed in the diagnostic clinics in Mora County.

It is recognized that syphilis in pregnancy ends in still-birth in 25 per cent of untreated cases, and that of live-born infants of syphilitic women, 20 per cent die in early infancy.⁴ Consequently since so many syphilitic pregnancies end in still-birth or neonatal deaths, one does not expect to find a high syphilis rate in young children. After the age of puberty the syphilis rate among children tends to rise due to acquired infection. In view of these facts, children of the youngest age group were not expected to show a very high percentage of syphilis. In the Mora County study only one child under six years of age was given the serological tests.

Table 2 gives the results of blood tests of 1,646 individuals classified by sex, age and serological tests for syphilis.

Of individuals between 6 and 12 years of age who were given the Wassermann and Kahn tests at the diagnostic clinics, 2.5 per cent gave clear positive reaction. This percentage may be compared with the estimated prevalence of syphilis among children in the United States generally, which is believed to be above 2 per cent. In such an age group, while some acquired syphilis may possibly be present, most of the cases are believed to be congenital in their origin. Of the total group of all ages over 12 years, the period of life when acquired syphilis becomes of increased importance, 6.2 per cent gave positive Wassermann or Kahn or both reactions. The highest percentage of positive reactions was in the age group from 31 to 40. In this group 12 per cent were found to have positive Wassermanns or Kahns or both. The females of this group showed a percentage of positives somewhat higher than the males, namely, 12.1 per cent for females, and 11.7 per cent for males. The next highest percentage was in the group from 41 to 50 years of age, which showed 10.4 per cent positive for both sexes.

A classification of the group over 17 years of age according to marital status and serological report is of interest and is presented in table 3.

Of the 1561 tests made on 282 single individuals of both sexes, 17 years of age and over, about 50 per cent were found to be positive; of 581 married men and women, over 17 years of age, 8.3 per cent had positive serological tests. Among the 85 divorced, widowed or separated individuals, 14.1 per cent had positive tests. Separated by sex and marital status, the single

TABLE II

Distribution of Blood Wassermann and Kahn Reactions of 1646 Individuals, by Age Groups and Sex

Male

Age Group	Total		Positive		Negative		Doubtful	
	No.	%	No.	%	No.	%	No.	%
6-11 years.....	93	12.8	2	2.1	90	96.8	1	1.1
12-21 years.....	295	40.5	6	2.0	288	97.6	1	0.4
22-30 years.....	107	14.7	13	12.2	91	85.0	3	2.8
31-40 years.....	77	10.6	9	11.7	67	87.0	1	1.3
41-50 years.....	70	9.6	11	15.7	58	82.9	1	1.4
51 and over.....	77	10.6	5	6.5	69	89.6	3	3.9
Not given.....	9	1.2	0	0	9	100.0	0	0
Total.....	728	100.0	46	6.3	672	92.4	10	1.3

Female

6-11 years.....	104	11.3	3	2.8	99	95.2	2	2.0
12-21 years.....	351	38.2	11	3.1	339	96.6	1	0.3
22-30 years.....	159	17.4	8	5.0	151	95.0	0	0
31-40 years.....	140	15.3	17	12.1	122	87.1	1	.8
41-50 years.....	84	9.1	5	5.9	78	92.9	1	1.2
51 and over.....	71	7.7	3	4.2	68	95.8	0	0
Not given.....	9	1.0	2	22.2	7	77.8	0	0
Total.....	918	100.0	49	5.4	864	94.1	5	0.5

Both Sexes

6-11 years.....	197	12.0	5	2.5	189	95.9	3	1.6
12-21 years.....	646	39.2	17	2.6	627	97.1	2	0.3
22-30 years.....	266	16.2	21	7.9	242	91.0	3	1.1
31-40 years.....	217	13.2	26	12.0	189	87.1	2	.9
41-50 years.....	154	9.3	16	10.4	136	88.3	2	1.3
51 and over.....	148	9.0	8	5.4	137	92.6	3	2.0
Not given.....	18	1.1	2	11.1	16	88.9	0	0
Total.....	1,646	100.0	95	5.8	1,536	93.3	15	0.9

males showed 7 per cent, and the single females 2.5 per cent positives. In the married group the males provided 8.9 per cent, and the females 7.9 per cent positives. These figures would lead one to believe, and quite correctly, that many women are infected in the sex relations of marriage. Syphilis is often a familial disease.

Some comments may be made upon the distribution of positive Wassermann or Kahn tests, according to occupational groups. Table 4 gives this information.

Of the total of 1,646 individuals tested for syphilis, 659 individuals of both sexes were attending school. In this group 1.8 per cent were found to have positive serological tests. Individuals engaged in housework numbered 378, and of these 8.2 per cent were positive. There were 344 men and women who described themselves as farmers, and of them 8.7 per cent were positive. Classified as "other occupations" were 212 persons of

TABLE III

Distribution of Blood Wassermann and Kahn Reactions of 1023 Individuals 17 Years of Age, and over, by Marital Status and Sex

Male

Marital Status	Total		Positive		Negative		Doubtful	
	No.	%	No.	%	No.	%	No.	%
Single.....	158	35.9	11	7.0	145	91.8	2	1.2
Married.....	214	48.7	19	8.9	191	89.2	4	1.9
Wid., Div. or Sep.....	23	5.2	4	17.4	18	78.3	1	4.3
Not given.....	44	10.2	4	9.1	39	88.6	1	2.3
Total.....	439	100.0	38	8.7	393	89.5	8	1.8

Female

Single.....	124	21.2	3	2.5	121	97.5	0	0
Married.....	367	62.9	29	7.9	336	91.5	2	0.6
Wid., Div. or Sep.....	62	10.6	8	13.0	54	87.0	0	0
Not given.....	31	5.3	4	12.9	27	87.1	0	0
Total.....	584	100.0	44	7.5	538	92.2	2	0.3

Both Sexes

Single.....	282	27.6	14	5.0	266	94.3	2	0.7
Married.....	581	56.8	48	8.3	527	90.7	6	1.0
Wid., Div. or Sep.....	85	8.3	12	14.1	72	84.7	1	1.2
Not given.....	75	7.3	8	10.7	66	88.0	1	1.3
Total.....	1,023	100.0	82	8.0	931	91.0	10	1.0

whom 8.0 per cent were positive. The highest percentage of positive Wassermann or Kahn were found among those who gave their occupation as school teachers. Of 53 teachers who submitted to the Wassermann and Kahn tests, 9.4 per cent were discovered to have positive reactions.

DISCUSSION

To what extent may the findings in Mora County be considered as representative of the Spanish-American population of New Mexico as a whole? It is believed that the 1,040 persons who had blood tests for syphilis were representative of the general Spanish-American population of this county. They were unselected and included an adequate number of males and females at all ages except children below six years. But the geographical location and the poor transportation facilities of Mora County, the absence of any large center of population may well lead to the supposition that the population of this county is more protected and less exposed to infection than the Spanish-American population of a more urban county. Everything considered, it seems probable that the prevalence of syphilis in certain parts of New Mexico is approximately the same as that discovered in Mora County. If experience elsewhere is applicable, the prevalence rate of

TABLE IV

Distribution of Blood Wassermann and Kahn Reactions of 1646 Individuals, by Occupation and Sex

Male

Occupation	Total		Positive		Negative		Doubtful	
	No.	%	No.	%	No.	%	No.	%
In school.....	323	44.3	7	2.2	314	97.2	2	0.6
Housework.....	0	0	0	0	0	0	0	0
Farmer.....	283	38.9	25	8.8	253	89.4	5	1.8
Teacher.....	26	3.6	3	11.5	23	88.5	0	0
Other.....	96	13.2	11	11.5	82	85.4	3	3.1
Total.....	728	100.0	46	6.3	672	92.2	10	1.5

Female

In school.....	336	36.6	5	1.5	328	97.6	3	.9
Housework.....	378	41.2	31	8.2	345	91.3	2	.5
Farmer.....	61	6.7	5	8.2	56	91.8	0	0
Teacher.....	27	2.9	2	7.4	25	92.6	0	0
Other.....	116	12.6	6	5.2	110	94.8	0	0
Total.....	918	100.0	49	5.3	864	94.1	5	.6

Both Sexes

In school.....	659	40.0	12	1.8	642	97.4	5	.8
Housework.....	378	23.0	31	8.2	345	91.3	2	.5
Farmer.....	344	20.9	30	8.7	309	89.8	5	1.5
Teacher.....	53	3.2	5	9.4	48	90.6	0	0
Other.....	212	12.9	17	8.0	192	90.6	3	1.4
Total.....	1,646	100.0	95	5.8	1,536	93.2	15	.9

Spanish-Americans in the towns and cities of the state is somewhat higher, and the 5.8 per cent prevalence of syphilis in Mora may well represent the minimum extent of the disease in the Spanish-American part of the population. If 60 per cent of the population of New Mexico is Spanish-American this would mean that, of the 250,000 Spanish-Americans, about 14,500 have syphilis.

In this connection it is of interest to compare the results of the survey in Mora County with serological studies in rural and village populations in other states. Of the male workers in a rural coal-mining community in West Virginia, 2372 Americans were 5.1 per cent and 778 foreign-born were 6.4 per cent positive. Physical examinations of several thousand men working in lead and zinc mines in Oklahoma and Kansas showed that 8 per cent were syphilitic. On the Cherokee Reservation, North Carolina, 1080 Indians serologically tested were 6 per cent positive. On the Klamath Reservation, Oregon, 5.9 per cent of the Indian inhabitants were presumably syphilitic. In a serological survey of 30,090 individuals in five rural Negro southern population groups in Mississippi, Alabama, Georgia, North

Carolina, and Tennessee, 8.7 per cent of all children under 15 years of age were found to be syphilitic (largely congenital); 26.2 per cent of females over 15 years were positive; and 24.5 per cent of males. In Mora County it will be remembered that the prevalence figure for the entire group was 5.8 per cent, and that, of these, children were 2.5 per cent positive, males over 12 years of age 6.9 per cent, and females 5.7 per cent positive.

CONCLUSION

A "thumb-nail" sketch of "*Sangre Impura* in Mora," would picture the predominantly Spanish-American population living under adverse hygienic and economic conditions, as having a high prevalence of subclinical Malta fever, constantly threatened by typhoid fever, and presenting syphilis as a serious health and medical problem. The facts regarding the prevalence and epidemiology of syphilis are such as might be expected in such a community, except that 5.8 per cent of the whole population infected is perhaps an unusually high rate for an isolated rural white population. The spread of syphilis by family contacts and by prostitution is the same as in many communities. However, the histories and clinical manifestations of syphilis in infected individuals reveal an unusual situation, namely, an almost complete lack of knowledge regarding this disease and its treatment, and virtually total absence of available medical care for the prevention of the late crippling and fatal manifestations of syphilis. The problem of medical care, then, is the most urgent one both for the preservation of the lives and health of infected individuals and for the prevention of the spread of syphilis, for by modern treatment syphilis in a majority of cases can be quickly rendered non-infectious.

In accordance with this principle, all persons in whom a diagnosis of syphilis was made in the course of this study were asked to report to the County Health Officer and to arrange for treatment, either as private patients or as recipients of medical relief under the state relief plan. The writer examined many of the infected individuals and advised with the Health Officer regarding their treatment. Of those who may be classified as private patients, there were very few indeed. Of the many classified as indigent patients, especially those in the early stages of the disease, a majority are now receiving competent treatment.

Improved economic conditions will greatly aid the efforts of the local and state medical and health authorities in providing adequate medical care and preventive measures in Mora County. Not only will individuals be better able to obtain medical care as private patients, but it is hoped that more adequate preventive medical and sanitary services may soon be instituted. Such measures can provide additional protection against Malta fever, can produce a great decrease in the prevalence of typhoid fever, and, most important of all, can prevent many of the disasters now attributable to syphilis.

REFERENCES

1. MITCHELL, C. A., and HUMPHREYS, F. A.: Serological diagnosis of brucelliasis, Canadian Pub. Health Jr., 1933, xxiv, 337-342.
2. REIMANN, H. A.: Malta fever; *in* MUSSER, J. H.: Internal medicine: its theory and practice, 1932, Lea and Febiger, Philadelphia, page 58.
3. ROSENAU, M. J.: Preventive medicine and hygiene, 1927, D. Appleton and Company, New York, page 105.
4. JEANS, P. C., and COOKE, J. V.: Prepubescent syphilis, 1930, D. Appleton and Company, New York, page 108.

EDITORIAL

THE EFFECT OF TOBACCO ON DISEASES OF THE BLOOD VESSELS

For many years physicians who have been particularly interested in vascular diseases have had a definite clinical impression that the smoking of tobacco, and particularly of cigarettes, has played some part in the etiology of thromboangiitis obliterans. Opinion has been divided, however, as to whether the use of tobacco was merely a contributing factor to the progress and symptoms, or whether it actually caused the vascular lesions. Statistics have shown a very low incidence of non-smokers among patients with this disease, less than 2 per cent in The Mayo Clinic series, compared with 26 per cent in the control group, and a high incidence of heavy smokers, 61 per cent compared with 26 per cent in the control group. In contrast, White and Sharber found no essential differences in consumption of tobacco by a large group of persons with angina pectoris when compared with their controls, although tobacco has been considered to have some relation to this syndrome also. Definite clinical improvement has been reported following cessation of the use of tobacco in many cases of thromboangiitis obliterans, and although the simultaneous use of rest and other therapeutic procedures may have been in part accountable for this, improvement has seemed less definite and relapses more frequent when smoking was continued.

Maddock and Collier have demonstrated vasoconstriction, as indicated by a fall of the cutaneous temperature of men during a test in which cigarettes were smoked, and this work has been corroborated in tests made on approximately two-thirds of a series of both normal men and patients with thromboangiitis obliterans at The Mayo Clinic. Vasoconstriction is an unfavorable influence in cases of arterial disease, not only thromboangiitis obliterans but the occlusive types of arteriosclerosis and the vasospastic disturbances as well. If the circulation is already badly impaired it is easy to see how repeated vasoconstriction may cause definite exacerbation of symptoms and even contribute to tissue destruction. This factor of vasoconstriction might explain a deleterious effect of tobacco in all types of vascular diseases, once they have developed, but fails to explain the low incidence of non-smokers and the high incidence of heavy smokers among patients with thromboangiitis obliterans.

The recent work of Harkavy and Sulzberger, and their respective co-workers, on hypersensitivity of the skin to extracts of tobacco has suggested another explanation of the relationship of tobacco smoking to thromboangiitis obliterans. Sulzberger found that 77 per cent of patients with this disease reacted positively, as compared with 36 per cent of a control series, and Harkavy found 56 per cent positive compared with only 20 per cent of controls. Granting that the extracts used were rather concentrated and that the patients tested were mostly of one race (Jewish), one cannot deny

the possible significance of this work. If, as Sulzberger has suggested, one considers thromboangiitis obliterans as an idiosyncratic or allergic disease, using "allergy" in its broadest sense, and if tobacco is the most common allergen, the relative rarity of the disease among the heavily smoking population as a whole is made compatible with the abnormally high incidence of smoking and heavy smoking among patients who are afflicted with it. The few non-smokers and persons not sensitive to tobacco may have an idiosyncrasy to some other irritants or even to some bacteria or their toxins. It is difficult, however, to conceive of the pathogenesis of the localized definite and permanent organic changes in the blood vessels as the result of allergic or even of idiosyncratic reactions. It is difficult to understand why they usually appear years after smoking was begun, and in spite of continuance of smoking may recur only at intervals of months or years. There is no precedent for the production of such a disease through idiosyncrasy to an inhalant. Possibly there is some analogy to idiosyncrasies to certain drugs. Further confirmation of Harkavy and Sulzberger's work among larger groups of patients of more varied nationalities is desirable.

There is certainly sufficient clinical and experimental evidence to warrant that patients with thromboangiitis obliterans be forbidden to use tobacco, whether one considers it as a mere vasospastic influence or as the fundamental cause of the lesions. However, let it be remembered that in the light of present knowledge thromboangiitis obliterans is only a pathologic entity the etiology of which may be multiple. Let it be remembered that some patients with proved thromboangiitis obliterans have never smoked tobacco, that a not inconsiderable number have used it sparingly, and that not all the patients tested have given positive skin tests to extracts of tobacco. If the percentage of possible chance positives is subtracted from the statistics of Sulzberger and Harkavy, respectively, there remain only 41 and 66 per cent of cases in which tobacco could be considered the primary factor. It should not be considered that the etiology of this interesting disease is definitely settled, and the minds of physicians should be kept open with regard to the possibility of other etiologic factors besides tobacco.

NELSON W. BARKER, M.D.

REVIEWS

The Practitioner's Library of Medicine and Surgery. Supervising Editor, GEORGE BLUMER, M.A. (Yale), M.D., F.A.C.P.; David P. Smith Clinical Professor of Medicine, Yale University School of Medicine; Consulting Physician to the New Haven Hospital. *Volume V: Traumatic Surgery.* Associate Editor, THEODORE S. MOÏSE, JR., B.A., M.D., Surgeon to the Eastern Maine General Hospital, Bangor, Maine. xlv + 1080 pages, 615 illustrations. *Volume VI: Obstetrics and Gynecology.* Associate Editor, LUTHER K. MUSSELMAN, B.S., Ph.D., M.D., Associate Clinical Professor of Obstetrics and Gynecology, Yale University School of Medicine. xlv + 900 pages, 312 illustrations. D. Appleton-Century Company, New York. 1934. Price, \$10.00 a volume.

The preceding four volumes of *The Practitioner's Library of Medicine and Surgery* have been reviewed in THE ANNALS as they have appeared. In sequence they dealt, respectively, with Anatomy and Physiology as Applied to Practical Medicine, The Technic of Physical and Laboratory Examination in Clinical Medicine, Practice of Medicine, and Non-Traumatic Surgery.

The fifth volume in the series, *Traumatic Surgery*, is the work of seventeen contributors. Very properly, trauma has been given a wide interpretation so that lesions of thermal, chemical, electrical, radioactive and parasitic etiology are considered, as well as those due to mechanical force. Traumatic Shock, Posttraumatic States and The Industrial Aspects of Medical Practice are the three concluding chapters of the seventeen into which this system is divided. For a work produced by so large a group of contributors, a uniformly high level of excellence has been attained to an unusual degree. The few readers who are expert in one or more of the fields discussed will consider the treatment of their special interests inadequate, but the internist who must have the essentials of traumatic surgery available, the general practitioner and the student will appreciate the direct, lucid style, the evident condensation and the well-chosen illustrations. Typography and make-up are alike excellent, and a very complete index is provided.

Volume VI is a system of *Obstetrics and Gynecology* in seventeen chapters by fourteen contributors. Of necessity, the treatment of these subjects follows the conventional form, beginning with the Physiology of Pregnancy and proceeding to the abnormal. More than usual attention has been given to the presentation of the pathology of the ovum and of gynecological conditions in general. The growing importance of teratology is thus recognized and this subject receives more attention than some standard texts on pathology were willing to grant it not so many years ago. As foretold in the preface, every effort has been made to set forth clearly that subject matter "which is preëminently of practical utility to the man in general practice." Those diagnostic procedures which forewarn of trouble, pelvimetry and fetal cephalometry, are for this reason treated very fully and excellently illustrated. The final chapter deals with the Relationship of Gynecology to the Specialties.

These two new volumes fully meet the standard set by those which preceded and can be recommended as presenting clearly and concisely material of proved value to the practitioner.

C. V. W.

Book Review. By ROX B. GIBSON, M.D., Associate Professor of Neurology, University of Chicago. xv + 272 pages, with 491 illustrations. Charles C. Thomas, Springfield, Ill., U.S.A. 1934. Price, \$8.50.

This book is a real and valuable addition to neurologic literature. The method of presenting the material in this concise and systematic manner in textbooks has been dispensed with.

The author's plan has been to "correlate certain biological data which are considered of importance to the study of the human nervous system in health and in disease." This he has done in an able manner. The average student's poor understanding of the subject is due largely to the current method of isolated and uncorrelated presentation of anatomy, physiology, and pathology. The author has brought these basic sciences together in a logical connected fashion. Diseases of the nervous system are presented as a disturbance of function due to definite pathological changes rather than the customary presentation of a group of signs and symptoms. One sees none of the "cataloguing" of nervous diseases so common in textbooks.

It is impossible to give a detailed account of the contents of such a work. The necessary anatomical and physiological data are presented either in special chapters or wherever necessary to clarify the subject under discussion. Each subdivision of the nervous system is ably accounted for in the thirty chapters. The chapters on reflexes, technic of neurological examination, intracranial tumors, vegetative nervous system, vascular diseases, and the epilepsies are outstanding.

The text is presented in a clear readable style. It contains a wealth of material with adequate well chosen illustrations. The bibliography contains over a thousand valuable titles. The index is accurate and well catalogued. The book is to be highly recommended to any serious student of neurology.

J. G. A., JR.

Handbook of Chemotherapy. By DR. VIKTOR FISCHL and PROF. DR. HANS SCHLOSSBERGER, Member of the Reich Board of Health, Berlin-Dahlem. English translation from the German by A. S. SCHWARTZMAN, A.B., M.D., Washington, D. C. *Part I. Metal-Free Organic Compounds.* xi + 410 pages; 18 × 25 cm. H. G. Roebuck and Son, Baltimore, Md. 1933. Price, \$8.00.

Workers in the field of pharmacology and its cognate sciences will welcome the appearance of this comprehensive treatise on chemotherapy. Accepting the term in its broadest significance, namely, the relation between chemical constitution and pharmacologic response, hitherto no exhaustive treatise of this kind has been published in the English language. Frankel's *Arzneimittel Synthese* and Ostwalt's work on chemical structure and pharmacologic activity have stood practically alone in the field.

This first volume which embraces the so-called "Metal Free" organic compounds is subdivided under twelve headings. These are Acyclic Chlorine Compounds, Unsaturated Fatty Acids, Benzol and Naphthalene Compounds, Amino Acids, Quinoline Derivatives, Quinine Derivatives, Emetine and Its Derivatives, Other Plant Substances, Acridin Derivatives, Other Dye Stuffs, Colorless Urea Derivatives and Serum of Man and Some Types of Apes.

It is quite evident from the foregoing arrangement of subject matter that the approach to this subject by these authors is through a classification according to chemical constitution. A typical example is that given in Chapter 3 under Benzol and Naphthalene Compounds. The first of these discussed is salicylic acid. Under this heading the history and occurrence of the compound are effectively described. This is followed by chemotherapeutic considerations of the isomerism of the hydroxybenzoic acids. Certain of the esters of salicylic acid useful in therapeutics are then developed. This chemical discussion precedes an exposition on the pharmacology, toxicology, and in many instances the practical therapeutics of the substances.

The authors have laid special stress on this particular classification and approach to chemotherapy. As set forth in the foreword, an effort has been made to eradicate the numerous mistakes which have crept into the literature of the last decades.

In the main, volume one fulfills the purpose of the authors; i.e., to present, in a well-classified, orderly style the subject matter of chemotherapy to the experimental worker in this field.

Most of the mechanical features of the volume are excellent; the printing for the most part is well done. The chemical formulae, of which the book contains many, show an inferior grade of workmanship. Typographical errors are surprisingly few in number. The enterprise of the publisher in undertaking this difficult work should be encouraged by scientific workers.

J. C. K., Jr.

Clio Medica—Chinese Medicine. By WILLIAM R. MORSE, M.D., LL.D., F.A.C.S. Edited by E. B. KRUMBHAAR, M.D. xxiii + 185 pages; 11.5 × 17 cm. Paul B. Hoeber, Inc. 1934. Price, \$2.50.

The history of Chinese medicine seems to be coming to the fore, for in 1932 there appeared from the Tientsin Press the large work by K. Chimin Wong, who was formerly lecturer on medical history at the National Central University, and Wu Lien-teh, director of the Manchurian Plague Prevention Commission. This large work has now been supplemented by this excellent little book, one of the justly popular Clio Series by William R. Morse, the dean of the Medical School of West China Union University.

The book very wisely starts off with an account of the Chinese natural philosophy and this is followed by an account of the Chinese gods of medicine and of the Chinese medical literature. Among others there is a chapter on the pulse, a matter of the greatest importance to the Chinese doctor, an account of surgery and a long and interesting study of the subject of acupuncture. The book is well illustrated. The charm of the little volume is greatly enhanced by quite a number of quotations, mostly from the Chinese sages, one of which is typical of the present day physicians and surgeons, who have no interest in medical history. It is from Lao Tzu: "Man is an infant born at midnight, who, when he sees the sunrise, thinks that yesterday never existed."

The book closes with a valuable bibliography. One cannot read this volume without being impressed by the greatness of the Chinese philosophy, no matter what we may think of their ancient and still persisting views of the healing art. It is a welcome addition to anyone's library.

J. R.

Wilhelm Conrad Röntgen and the Early History of the Roentgen-Rays. By OTTO GLASER, with a Chapter, Personal Reminiscences of W. C. Röntgen, by MARCOUS BOVERI. xii + 494 pages; 20 × 25 cm. Charles C. Thomas. 1933. Price, \$6.00.

It seems fitting that Röntgen, who opened up a new field in medicine and science, should have a most excellent biographer to record the story of his achievement. Otto Glaser of the Cleveland Clinic Foundation has done a magnificent piece of work which may serve as a model for other future medical biographers. Röntgen, with his then rare degree of Doctor of Medicine of the University of Würzburg, takes his place with the medical men of super achievements.

The book first appeared in German in 1931, from the Springer Press, and now the English edition is most welcome. The book starts out with the discovery of the roentgen-rays, and with the scientist's preliminary communication, "On a new kind of ray," first made known to the world by the announcement and Röntgen's lecture before the Physical Medical Society in Würzburg. Then follows a most interesting account of Röntgen's career in a fairly readable style. One of Röntgen's most intimate friends, and indeed a devoted follower, was greatly aided by Boveri's wife and by his daughter, Mrs. Margarete Boveri, who has contributed a chapter of personal reminiscences, and a few pages on other things which give the reader what may be regarded

as an accurate and intimate knowledge of the man and how he lived and felt. There is a well edited collection of what was written in the daily press and in magazines, much of this very amusing. Then practically every phase of roentgen-ray work is gone into. These chapters are full of important information, some of it chiefly interesting to those familiar with the rays but all set forth with praiseworthy clarity.

There are short stories of the pioneers in the use of the rays, some of these men, martyrs to it, as the danger of the emanations was not recognized until a considerable number of investigators had been badly and often fatally injured. The book closes with a bibliography listing over a thousand books and articles. It is impossible to speak of this book in terms which are too enthusiastic. It is accurate, readable, interesting and contains the historical records of one of the greatest of the discoveries which has influenced man and medicine. It should be in the library of every roentgenologist and every doctor. If you miss it you will be missing one of the best of the medical, or if you insist scientific, biographies.

J. R.

A System of Clinical Medicine. By THOMAS DIXON SAVILL, M.D.; edited by AGNES SAVILL, M.D., assisted by E. C. WARNER, M.D. Ninth edition. xxx + 1063 pages; 16.5 × 23.5 cm. William Wood and Company, Baltimore. 1933. Price, \$9.00.

This work differs from the usual medical textbook in that its plan of organization is based on the presenting symptoms of disease, instead of the usual grouping by etiological factors and body tracts. This allows emphasis to be given to differential diagnosis. In his introduction to the first edition, the author states: "The subject will be approached from the standpoint of symptomatology. The principle throughout will consist of tracing from effect (symptoms) to cause (the morbid cause in operation)."

This system has been well carried out. The book is much more coherent and readable than most books on differential diagnosis, though not as complete. Conditions which are primarily surgical have been largely omitted. A concise but well detailed description of a disease picture is presented, usually in the section devoted to its leading symptom. Symptoms which are classified in other sections are described briefly, and reference given to the leading article in its proper part of the book. Cross references are quite complete.

In the present edition, fifteen contributors have revised or rewritten many sections of the book, without deviating noticeably from the original plan. It is inevitable that some unevenness in the quality of the contributions should occur; usually they are uniformly good.

Terminology is at times different from that ordinarily employed in this country; the older terms for types of nephritis, for example, are retained, without mention of the more modern nomenclature which is becoming popular at present.

The section on diseases of the nervous system is very complete, taking up 260 pages. The general plan of the book is especially fortunate when applied in this field, as few neurological textbooks are arranged to facilitate diagnosis. This section, as are most, is well supplied with tables summarizing differential diagnosis. The chapter on diseases of the skin (60 pages) is also well arranged and should be useful.

Treatment suggested is at times not up-to-date. Thus in lead poisoning, no treatment to promote storage of lead in bone is suggested, and the use of potassium iodide is recommended in all cases. Digitalis is recommended in all cases of pneumonia, whereas serum and oxygen are mentioned very superficially.

In general, this book gives the impression that it should be very useful to students and practitioners. Because of its unusual arrangement, liberal supply of differential tables, and completeness, it should also be helpful to teachers.

T. N. C.

COLLEGE NEWS NOTES

AMERICAN COLLEGE OF PHYSICIANS

ELECTIONS

1934-1935

(Chicago, April 19, 1934)

Jonathan C. Meakins, Professor of Medicine and Director of the Department of Medicine, McGill University Faculty of Medicine, Montreal, Canada, ascended to the Presidency of the College April 19, 1934.

President-Elect James Alex. Miller, New York, N. Y.
First Vice-President James H. Means, Boston, Mass.
Second Vice-President Randolph Lyons, New Orleans, La.
Third Vice-President James F. Churchill, San Diego, Calif.

Board of Regents

(Term Expiring 1937)

George Morris Piersol, Philadelphia, Pa.
William J. Kerr, San Francisco, Calif.
Roger I. Lee, Boston, Mass.
Sydney R. Miller, Baltimore, Md.
G. Gill Richards, Salt Lake City, Utah

Board of Governors

(Term Expiring 1937)

Fred W. Wilkerson Alabama—Montgomery
W. Warner Watkins Arizona—Phoenix
Lewi. B. Flinn Delaware—Wilmington
Turner Zeigler Cason Florida—Jacksonville
William R. Houston Georgia—Augusta
James G. Carr (Northern) Illinois—Chicago
Ernest B. Bradley Kentucky—Lexington
Edwin W. Gehring Maine—Portland
Henry M. Thomas, Jr. Maryland—Baltimore
G. W. F. Rembert Mississippi—Jackson
Lester H. Fegelman Montana—Helena
LeRoy S. Peters New Mexico—Albuquerque
Robert A. Cooke (Eastern) New York—New York
A. B. Brewster Ohio—Dayton
C. Herbert Conlen Oregon—Portland
Charles J. Stone Texas—Galveston
Mark S. Carter Wisconsin—Wauwatosa
Hector K. Alvord Puerto Rico—San Juan
Robert A. Collins Manitoba—Winnipeg, Canada

(Term Expiring 1936)

Robert L. Kerr New Hampshire—Manchester
Charles E. A. Smith New Jersey—Atlantic City

(Term Expiring 1935)

William B. Breed	Massachusetts—Boston
Louis E. Viko	Utah—Salt Lake City

Ex Officio

Perceval S. Rossiter	United States Navy
----------------------------	--------------------

CHICAGO CLINICAL SESSION

The Eighteenth Annual Clinical Session of the American College of Physicians was held in Chicago, Ill., April 16–20, 1934. Physicians were in attendance from every State of the United States, with the exception of Nevada, from the Provinces of Alberta, Ontario, Saskatchewan and Quebec, Canada, from China, Austria, Germany and Mexico. The total recorded registration was 2,070, of which number 1,342 were registered physicians, 420 senior medical students, 192 exhibitors and 116 ladies.

Abstracted Minutes of the meetings of the Board of Regents, Board of Governors and the General Business Meeting will appear in the June number. However, we publish herewith the list of physicians elected to Associateship and to Fellowship during the Chicago Session. These lists do not include those elected during 1933, said list having been published in the January 1934 issue of this journal.

Elections to Associateship, April 15, 1934

Name	Address
Aaron, Francis A.	Pittsburgh, Pa.
Abramson, David Irvin	Brooklyn, N. Y.
Argy, William P., Jr.	Washington, D. C.
Askey, John Martin	Los Angeles, Calif.
Bair, George Elmer	Braddock, Pa.
Banks, Horace McMurran	Indianapolis, Ind.
Barry, Michael William	Omaha, Nebr.
Benner, Norman R.	Johnsonburg, Pa.
Booth, George	Pittsburgh, Pa.
Buckles, Maurice Gray	Waverly Hills, Ky.
Campbell, Edward Everett	Columbus, Ohio
Canelo, Clarence Kelly	San Jose, Calif.
Cate, William Robert	Nashville, Tenn.
Chapman, Edward Northrop	Colorado Springs, Colo.
Clark, Cyrus J.	Indianapolis, Ind.
Clawson, Thomas Alfred, Jr.	Salt Lake City, Utah
Colmore, Henry Perrine	San Juan, P. R.
Cooksey, Warren B.	Detroit, Mich.
Costa-Mandry, Oscar	San Juan, P. R.
Davies, Williard J.	Rockville Center, N. Y.
Denny, Earl Rankin	Tulsa, Okla.
Dessoff, Samuel	Washington, D. C.
Duggan, Le Roy Bates	Houston, Texas
Ensign, Dwight C.	Detroit, Mich.
Fearon, Henry Dana, Jr.	Brooklyn, N. Y.
Fischer, Carl Castle	Philadelphia, Pa.
Fopeano, John Vincent	Ann Arbor, Mich.
Fordham, George	Powellton, W. Va.
Gilbert, Joseph Pilmoor	Nashville, Tenn.

Givhan, Edgar Gilmore, Jr.	Birmingham, Ala.
Goodwin, Rufus Quitman	Oklahoma City, Okla.
Gott, John Richard, Jr.	Louisville, Ky.
Greenstein, Jacob	Providence, R. I.
Hadley, Ernest Elvin	Washington, D. C.
Hall, Augustus Alonzo	Columbus, Ohio
Hawkins, Leland Potts	Los Angeles, Calif.
Heintzelman, John Herbert Leyda	Pittsburgh, Pa.
Hines, Edgar Alphonso, Jr.	Rochester, Minn.
Hodges, Alfred Brown	Norfolk, Va.
Hoffman, Richards Holmes	Bellefonte, Pa.
Howe, Harland Fallis	Toledo, Ohio
Hoyt, Lyman H.	Boston, Mass.
Hubbard, Wilder Walton	Nashville, Tenn.
Hull, Edgar	New Orleans, La.
Johnston, Charles Louis	Catawissa, Pa.
Kennedy, Frank Sparling	London, Ont.
Kimball, Stockton	Buffalo, N. Y.
Kinkad, Kyle Johnston	Birmingham, Ala.
Kirklin, Oren Leslie	Rochester, Minn.
Kitzmiller, Karl V.	Cincinnati, Ohio
Knowles, George Milton	Hackensack, N. J.
Koppisch, Enrique	Miramar, San Juan, P. R.
Kuhl, Albert Franklin	Dayton, Ohio
Lambert, Luther Rush	Fairmont, W. Va.
Long, Henry Clay	Knoxville, Tenn.
Marble, Alexander	Boston, Mass.
Misko, George Harold	Lincoln, Nebr.
Modern, Fred S.	Los Angeles, Calif.
Moon, Arthur Ernest	Temple, Texas
Murray, Harold A.	Newark, N. J.
Neely, John Marshall	Lincoln, Nebr.
Nissen, Leonard M.	Livingston, N. Y.
Palmer, Harold Dwight	Rockford, Ill.
Perce, Carleton Barnhart	Ann Arbor, Mich.
Pinto, Juan Antonio	Rio Piedras, P. R.
Rod, E. Burkett	Lincoln, Nebr.
Rouland, Otto Andrew George	Lincoln, Nebr.
Rever, William S.	Detroit, Mich.
Reynolds, John Andrew	Longmeadow, Mass.
Rodriguez-Molina, Rafael	San Juan, P. R.
Rosenau, James Parks	Winston-Salem, N. C.
Schubert, William Ward, Jr.	Oklahoma City, Okla.
Shelton, Richard Olney	Birmingham, Ala.
Shelton, William J.	Pomona, N. Y.
Shelton, Irving William	Boston, Mass.
Shelton, Philip J.	New York, N. Y.
Shelton, Samuel I.	Dallas, Texas
Shelton, Samuel Clifton	Tulsa, Okla.
Shelton, Samuel I.	Louisville, Ky.
Shelton, Samuel I.	Hamover, N. H.
Shelton, Samuel I.	Calderwood, Tenn.
Shelton, Samuel I.	New Orleans, La.

Trump, Frank A.	Ottawa, Kan.
Ungerleider, Harry Eduarde	New York, N. Y.
Van Leuven, Buell H.	Petoskey, Mich.
Voke, Edward Lawrence	Akron, Ohio
Washburne, Annette Clarke	Madison, Wis.
Watson, Robert Briggs	Knoxville, Tenn.
Westcott, Franklin Howard	New York, N. Y.
White, Thomas Joseph	Jersey City, N. J.
Wilcox, Clark Anson	Wichita Falls, Texas
Wilson, Redford Alexander	Tucson, Ariz.
Wilson, Thomas Epps, Jr.	Jackson, Miss.
Wiseman, Bruce Kenneth	Columbus, Ohio
Woodard, James Madison	Aurora, Nebr.
Woodard, Paul Albert	Galveston, Texas

Elections to Fellowship, April 15, 1934

Name	Address
Altschul, Frank Joseph	Long Branch, N. J.
Altshuler, Samuel Simon	Detroit, Mich.
Bock, George Frederic	Watertown, N. Y.
Boutwell, Horace Keith	Brookline, Mass.
Bower, George Cummings	Marcy, N. Y.
Bowers, James Michael	Seattle, Wash.
Brown, Alan	Toronto, Ont.
Cabot, Irving Lyman	Brooklyn, N. Y.
Carr, Earl Curtis	M. C., U. S. Navy
Carroll, William E.	Meriden, Conn.
Chillingworth, Felix Percy	Boston, Mass.
Clarke, Charles Walter	New York, N. Y.
Cross, Sumner H.	Jenkintown, Pa.
Dana, Winfred Petersen	M. C., U. S. Navy
Drennan, Fred Miller	Chicago, Ill.
Duncan, Dean H.	Shreveport, La.
Dunlap, Harold Foster	Indianapolis, Ind.
Duryee, A. Wilbur	New York, N. Y.
Elghammer, H. William	Chicago, Ill.
Fancher, James Kenneth	Atlanta, Ga.
Fenger, Ejvind P. K.	Oak Terrace, Minn.
Funk, Victor K.	Oak Terrace, Minn.
Geraghty, Francis Joseph	Baltimore, Md.
Gibson, George Gordon	Wilkinsburg, Pa.
Goldberg, Samuel J.	New Haven, Conn.
Hall, William E.	Meriden, Conn.
Hanzlik, Paul John	San Francisco, Calif.
Heninger, Ben Rufus	New Orleans, La.
Hill, William Edward	Naugatuck, Conn.
Holbrook, J. Howard	Hamilton, Ont.
Jackson, Byron Hubbard	Scranton, Pa.
Jarman, Miletus Brown	Hot Springs, Va.
Jenkins, William Nathan	Port Gibson, Miss.
Kurtz, Chester Mott	Madison, Wis.
Lashmet, Floyd Heaton	Ann Arbor, Mich.
Makepeace, True E.	Farmington, Maine

Mayer, Orlando Benedict	Columbia, S. C.
Moyer, Torrence C.	Lincoln, Nebr.
Nelson, Luther Townsend	Portland, Ore.
Newcomb, William Bradford	Norfolk, Va.
Palmer, Harold W.	Wichita, Kan.
Palmer, Robert Sterling	Boston, Mass.
Piotzer, Roy G.	Buffalo, N. Y.
Price, A. Hazen	Detroit, Mich.
Quirk, John T.	Piqua, Ohio
Read, Hilton Shreve	Atlantic City, N. J.
Read, James Seay	Nashville, Tenn.
Ripps, Maurice L.	Elizabeth, N. J.
Rouse, Milford Owen	Dallas, Texas
Schwab, Edward Henry	Galveston, Texas
Shook, Hubert H.	Cincinnati, Ohio
Smith, E. Sanborn	Kirksville, Mo.
Smith, Walter Fox	Watertown, N. Y.
Stites, Frank Montgomery, Jr.	Louisville, Ky.
Strauss, Norman	New York, N. Y.
Striker, Cecil	Cincinnati, Ohio
Suarez, Ramon Miguel	Santurce, San Juan, P. R.
Tonkin, Harold Lazarus	Williamsport, Pa.
Wadburn, James Murray	Chicago, Ill.
Weinberg, Max. H.	Pittsburgh, Pa.
Willerton, William Velpoe	Montgomery, W. Va.
Wilson, Harry Hufts	Los Angeles, Calif.
Wright, Irving Sherwood	New York, N. Y.
Yatema, Stuart	Saginaw, Mich.
Young, George J.	Morristown, N. J.

PHILADELPHIA SELECTED FOR 1935 MEETING PLACE

From invitations of a number of cities, the Board of Regents of the American College of Physicians has accepted the invitation of Philadelphia for its Nineteenth Annual Clinical Session during 1935. The last previous meeting of the College held in Philadelphia was during 1923. Since that time, not only has the College made great strides in its development and influence, but the City of Philadelphia has added greatly to its medical facilities. The University of Pennsylvania has added a number of new buildings and laboratories and a new Graduate Hospital; Jefferson Medical College has added new laboratories and additions to its hospital; Temple University and the Woman's Medical College have both had entirely new buildings constructed for their medical schools. Many preeminent men in American medicine are connected with Philadelphia institutions. The facilities are so great and the interest so great that the College should be assured of one of the greatest sessions in its history. News of the appointment of the General Chairman and the subject of the meeting will appear in the next issue of this journal.

COLLEGE LIBRARY

As a result of the following gifts to the College Library of publications, it is again emphasized that any or all of the Fellows or members of the College who are interested in books are invited to donate an auto-

graphed copy to the College Library, which is founded, more or less, as a memorial to its members. The Library consists only of publications by its own members, there being no adequate reason at present to develop an extensive general library, other than one of a selective type as above mentioned.

Dr. John V. Barrow (Fellow), Los Angeles, Calif.—2 reprints;
Dr. Milton A. Bridges (Fellow), New York, N. Y.—1 reprint;
Dr. Glenville Giddings (Fellow), Atlanta, Ga.—1 reprint;
Dr. Frederick R. Taylor (Fellow), High Point, N. C.—1 reprint;
Dr. Mark Gerstle, Jr. (Associate), San Francisco, Calif.—7 reprints;
Dr. Herbert T. Kelly (Associate), Philadelphia, Pa.—1 reprint;
Dr. Frank S. Kennedy (Associate), London, Ont.—1 reprint;
Dr. Horace P. Marvin (Associate), Honolulu, T. H.—4 reprints;
Dr. George W. Parson (Associate), Texarkana, Tex.—1 reprint;
Dr. Francis J. Scully (Associate), Hot Springs Nat'l Park, Ark.—2 reprints;
Dr. E. S. Wegner (Associate), Lincoln, Nebr.—1 reprint.

DR. BAILEY K. ASHFORD HONORED

Dr. Bailey K. Ashford (Fellow), Founder of the School of Tropical Medicine of Puerto Rico, and for many years its Professor of Tropical Medicine and Mycology, was recently honored by the Island Legislature by having a statue-bust sculptured and placed in the main hall at the entrance to the school.

Dr. Ashford was elected Governor of the College for Puerto Rico at the last Clinical Session in Chicago.

Dr. John P. Zohlen (Fellow), Sheboygan, Wis., has been elected President of the Sheboygan Clinic and President of the Sheboygan County Medical Society.

"Clinical Amebiasis" was the subject of a lecture given by Dr. John V. Barrow (Fellow) at Santa Barbara, Calif., March 12, 1934, and also at Visalia, Calif., March 25, at the respective County Medical Meetings for these districts.

Dr. E. L. Whitney (Fellow), Walla Walla, Wash., addressed the Nez Perce County Medical Society at Lewiston, Idaho, March 21, 1934, on "Arterial Hypertension."

Dr. Herbert T. Kelly (Associate), Philadelphia, Pa., addressed the Bucks County Medical Society at Washington's Crossing, Pa., April 11, on "Metabolism and Diet in the Pneumonias."

Dr. A. B. Landry (Associate), Hartford, Conn., has been elected President of the Hartford County Medical Association for 1934-1935.

Dr. Frank S. Kennedy (Associate) has gone from The Mayo Clinic to London, Ont., Canada, where he has opened his office for the practice of Internal Medicine.

OBITUARY

DR. JOSEPH BRINGHURST

Dr. Joseph Bringhurst (Associate), died February 6, 1934, at his home at Felton, Delaware, following a stroke of paralysis a few days before.

Dr. Bringhurst attended Friends School, Swarthmore College, and later in 1898 graduated from the University of Pennsylvania School of Medicine. He practiced in and around West Chester for some years. At the outbreak of the World War, he entered the military service and was stationed at Camp Dix, New Jersey. He attained the rank of captain in the Medical Corps of the U. S. Army. After the war, he returned to Harrington, Delaware, and later moved to Felton.

Dr. Bringhurst was local surgeon to the Pennsylvania Railroad Company. He was a member of the medical board and lecturer in medicine to nurses at the Milford Emergency Hospital. He was a member and the secretary of the Kent County Medical Society, a member of the Medical Society of Delaware, a Fellow of the American Medical Association and a member of the Pennsylvania Railroad Surgeons Association. He became an Associate of the American College of Physicians during 1925.

LEWIS B. FLINN, M.D., F.A.C.P.

Reprint April 1934 issue, page 1201, line 11, Warren Shields change to Shields Warren; page 1215, reference 3, Shields, W. change to Warren, S.

NATIONAL HAY FEVER ANTIGENS



National Ragweed Antigen is standardized in nitrogen units. 1 nitrogen unit = 50 to 300 pollen units; this standardization makes for uniform potency and enables proper doses to be given of minimum bulk according to the need of the individual patient. Fixed, or set, doses cannot give the selectivity of required dose.

Successful Treatment of Hay Fever depends on diagnosis of the pollens responsible for allergic disturbances, a proper interpretation of the case history and use of the indicated Antigen in properly graduated doses. National Pollen Test Antigens are standardized extracts for determining, by the "intradermal" or "scratch test," the pollens responsible for sensitization, grouped according to area and season of pollination.

Ragweed Antigen for Treatment of Fall Hay Fever

Complete Treatment (24 doses) in 5 cc. Ampul-vials

V 209	{ Series "AA" 125 nitrogen units (8 doses)	\$8.50
	{ Series "A" 250 nitrogen units (8 doses)	
	{ Series "B" 500 nitrogen units (8 doses)	



We offer the above Special Outfit, for diagnosis and treatment of Fall Hay Fever, containing two diagnostic tests, 1 ampul-vial each of Series "AA," "A" and "B" Ragweed Antigen; 25 cc. ampul-vial of Sterile Salt Solution, for dilution of Antigen if needed; 25 cc. ampul-vial of Epinephrin 1-1000, to control local or systemic reactions.

V 216 Ragweed Antigen Outfit complete, \$10.00

THE NATIONAL DRUG COMPANY

PHILADELPHIA
U.S.A.



Mail Hay Fever and Poison Ivy Antigen Brochures per Annals of Internal Medicine.

Name Date.....

*Your Patients on Low Carbo-
hydrate Diets Will Appreciate*

CURDOLAC FOODS

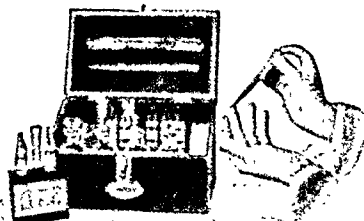
Curdolac Breakfast Cereal
Curdolac Soya Flour
Curdolac Wheat-Soya Flour
Curdolac Soya Cereal Johnny Cake
Flour
Curdolac Soya-Bran Breakfast Food
Curdolac Soya-Bran Flour
Cakes, Cookies

*Palatable—Nutritious
Satisfying*

Samples and Literature
on Request

CURDOLAC FOOD CO.
Box 299 - - Waukesha, Wis.

LAMOTTE Blood Chemistry SERVICE



For rapid esti-
mation of blood
sugar in deter-
mining sugar
tolerance of dia-
betic patient.

Uses only few
drops of finger
blood.

Permits tests at
close intervals.

LaMotte Blood Sugar Outfit

Invaluable for infant cases.

Accurate to 10 mg. of sugar per 100 c.c. of blood.

Direct result without calculations.

Only 20 minutes required for complete test.

Complete with instructions, price \$24.00, f.o.b. Balti-
more, Maryland.

LaMotte Blood Chemistry Service includes a series of
similar outfits for conducting the following accurate
tests.

Blood Urea—Icterus Index—Phenolsulphon-
phthalein—Urine pH—Blood pH—Gastric
Acidity—Calcium Phosphorus—Blood Bro-
mides—Urinalysis.

*If you do not have a LaMotte Blood Chemistry
Handbook, write today for a complimentary copy*

LaMotte Chemical Products Co.
418 Light Street - - - Baltimore, Md.

A Pure, Palatable, Carbonated

PREPARED WATER

THERE are many conditions,
no doubt, where you will
want your patient to increase
his daily intake of water.

In such cases, why not suggest
the use of Kalak Water, the pal-
atable, carbonated alkaline
water prescribed by physicians
for over twenty years.



Kalak Water is made
of carbonated distilled
water and chemically
pure salts of calcium
bicarbonate, sodium
chloride, sodium
phosphate and lit-
mus. It is a
very palatable and
refreshing

Kalak

The WYATT CLINIC

for

Chronic Arthritis



TUCSON, ARIZONA

The Potts Memorial Hospital, Inc.

Livingston, Columbia Co., New York

One hundred miles north of
New York City.

Forty miles south of Albany.

Private rooms for the reception of patients who have undergone phrenicectomy, artificial pneumothorax, or thoracoplasty; also minimal and moderately advanced cases of tuberculosis needing bed care. Rate \$25.00 per week.

There are openings, from time to time, for quiescent and arrested cases of tuberculosis who need rehabilitation treatment. Graduated work, under medical supervision, in Printing, Gardening, Poultry Raising, Nursing, Clerical and Domestic work for men and women between the ages of eighteen and fifty. Pleasant surroundings and the best of care make this an ideal place to complete the cure. Descriptive brochure, giving rates, will be sent upon request.

H. A. PATTISON, M.D., *Director*

L. M. NIESEN, M.D.,

Resident Physician

Hospital Consultation and Advisory Service

The products of the hospital are the cured patient, the proficient clinician, the well-trained nurse, and effective educational propaganda for the prevention of disease. In the evaluation of the hospital's accomplishment the accurate appraisal of *quality* performance is of more vital significance than is the volume of service rendered.

Office of

WILLIAM HENRY WALSH, M.D.

612 North Michigan Avenue

CHICAGO

PROFESSIONAL PROTECTION



MORE THAN
42,000 CLAIMS
AND SUITS
SUCCESSFULLY
HANDLED

THE

MEDICAL PROTECTIVE COMPANY

OF FORT WAYNE, INDIANA

WHEATON, ILLINOIS

THE AMERICAN COLLEGE OF PHYSICIANS

MEMBERS OF THE BOARD OF GOVERNORS

Term Expiring 1935

EGERTON L. CRISPIN.....	SOUTHERN CALIFORNIA—Los Angeles
GERALD B. WEBB.....	COLORADO—Colorado Springs
HENRY F. STOLL.....	CONNECTICUT—Hartford
WALLACE M. YATER.....	DISTRICT OF COLUMBIA—Washington
ERNEST E. LAUBAUGH.....	IDAHO—Boise
SAMUEL E. MUNSON.....	Southern ILLINOIS—Springfield
ROBERT M. MOORE.....	INDIANA—Indianapolis
THOMAS TALLMAN HOLT.....	KANSAS—Wichita
WILLIAM B. BREED.....	MASSACHUSETTS—Boston
ADOLPH SACHS.....	NEBRASKA—Omaha
ALLEN A. JONES.....	Western NEW YORK—Buffalo
LEANDER A. RIELY.....	OKLAHOMA—Oklahoma City
EDWARD J. G. BEARDSLEY.....	Eastern PENNSYLVANIA—Philadelphia
E. BOSWORTH MCCREADY.....	Western PENNSYLVANIA—Pittsburgh
JOHN O. MANIER.....	TENNESSEE—Nashville
LOUIS E. VIKO.....	UTAH—Salt Lake City
IAELZ H. ELLIOTT.....	ONTARIO—Toronto, Canada
WILLIAM M. JAMES.....	PANAMA and the CANAL ZONE

Term Expiring 1936

OLIVER C. MELSON.....	ARKANSAS—Little Rock
HANS LISSER.....	Northern CALIFORNIA—San Francisco
TOM BENTLEY THROCKMORTON.....	IOWA—Des Moines
JOSEPH E. KNIGHTON.....	LOUISIANA—Shreveport
JAMES D. BAUGH.....	MICHIGAN—Ann Arbor
EDWARD L. TERRY.....	MINNESOTA—Duluth
A. GOMINGO GRIFFITH.....	MISSOURI—Kansas City
ROBERT B. KEEL.....	NEW HAMPSHIRE—Manchester
CLARENCE L. ANDREWS.....	NEW JERSEY—Atlantic City
CHARLES HARTWELL COOKE (Vice Chair- man).....	NORTH CAROLINA—Asheville
JAMES D. ANDERSON.....	NORTH DAKOTA—Bismarek
ALEXANDER M. BURGESS.....	RHODE ISLAND—Providence
FORREST WILSON, JR.....	SOUTH CAROLINA—Charleston
CLARENCE H. BECHER.....	VERMONT—Burlington
L. MORSE DE HENNINGSEN.....	VIRGINIA—Richmond
HERBERT FORTY.....	WASHINGTON—Seattle
JOHN N. SIMPSON.....	WEST VIRGINIA—Morgantown
D. SCOTLAND LAWTON.....	QUEBEC—Montreal, Canada

Term Expiring 1937

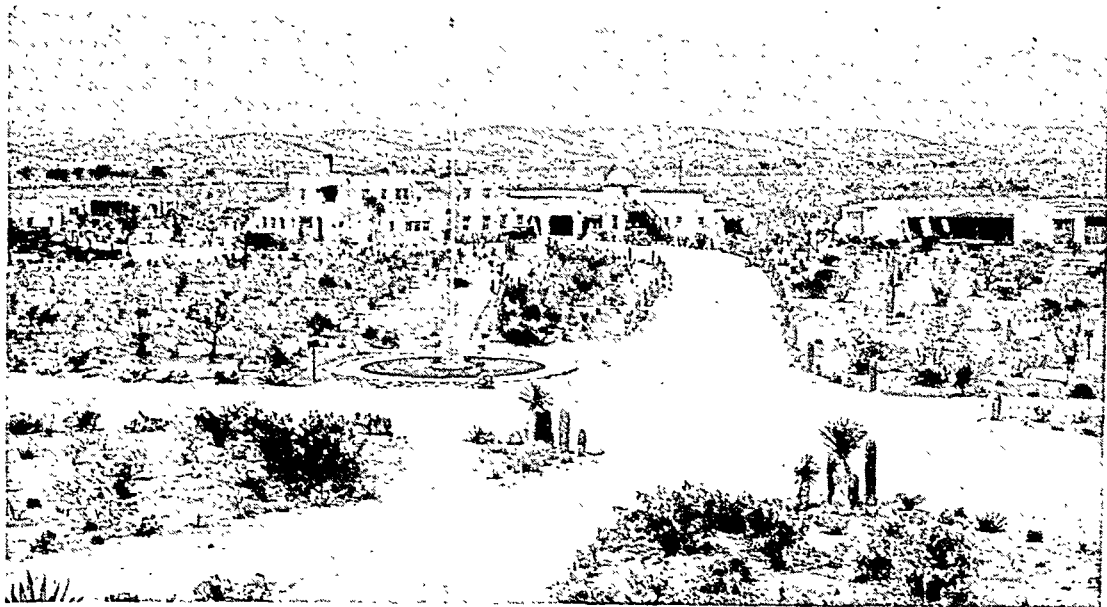
PAUL W. WHEATON.....	ALABAMA—Montgomery
W. WENDE WATKINS.....	ARIZONA—Phoenix
LOUIS B. FLEMING.....	DELAWARE—Wilmington
THOMAS T. CASPER.....	FLORIDA—Jacksonville
ARTHUR K. HODGSON.....	GEORGIA—Augusta
JAMES H. CASE.....	Northern ILLINOIS—Chicago
JOHN E. BENTLEY (Chairman).....	KENTUCKY—Lexington
CHARLES W. GIBSON.....	MAINE—Portland
JOHN M. THOMAS, JR.....	MARYLAND—Baltimore
W. K. H. STANLEY.....	MISSISSIPPI—Jackson
JOHN H. LUTHER.....	MONTANA—Helena
JOHN S. PETERSON.....	NEW MEXICO—Albuquerque
JOHN A. HARRIS.....	Eastern NEW YORK—New York
W. B. GIBSON.....	OHIO—Dayton
JOHN A. GIBSON.....	OREGON—Portland
JOHN A. GIBSON.....	TEXAS—Galveston
JOHN A. GIBSON.....	WISCONSIN—Wauwatosa
JOHN A. GIBSON.....	PORTO RICO—San Juan
JOHN A. GIBSON.....	MANITOBA—Winnipeg, Canada

Life Officers

JOHN A. GIBSON.....	United States Army
JOHN A. GIBSON.....	United States Navy
JOHN A. GIBSON.....	United States Public Health Service

The Desert Sanatorium and Institute of Research

Tucson, Arizona



Altitude 2,600 feet

Entering upon its eighth season, this well-known Institution affords the facilities of modern diagnosis and treatment under unexcelled climatic conditions. Its appointments represent the acme of attractiveness, comfort and convenience. Not a hospital for the treatment of pulmonary tuberculosis, it aims at the utmost perfection of diagnosis and treatment of every condition that may be benefited by a warm, dry, sunny climate of desert type, such as chronic arthritis, sinusitis, nontuberculous pulmonary and upper respiratory complaints, arterial hypertension, cardiorenal insufficiency, etc.

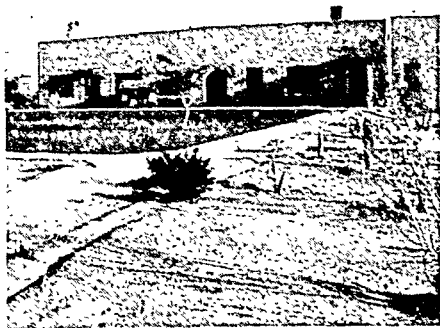
ALLEN K. KRAUSE, M.D., *Director*

W. PAUL HOLBROOK, M.D., *Physician-in-Chief*

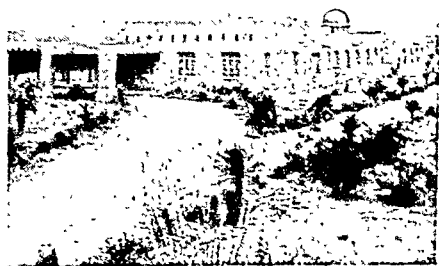
VIVIAN TAPPAN, M.D., *In Charge of Pediatrics*

MAX PINNER, M.D., *Director of Laboratories*

CHARLES W. MILLS, M.D., *In Charge of Visiting Staff*



Recreation Centre



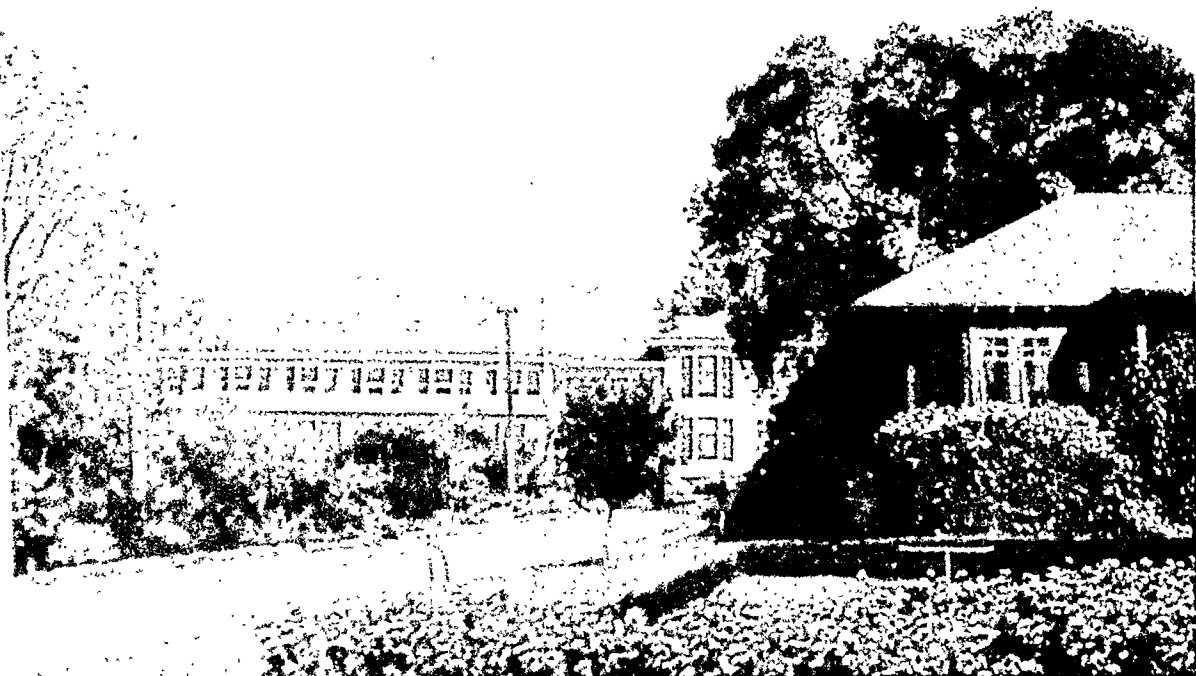
Out-Patient Clinic

WRITE FOR BOOKLET

For RATES AND OTHER INFORMATION
Address Secretary, Desert Sanatorium
Tucson, Arizona

THE POTTENGER SANATORIUM AND CLINIC FOR DISEASES OF THE CHEST

Monrovia, California



THIRTY YEARS' EXPERIENCE IN THE TREATMENT OF TUBERCULOSIS

LOCATION

Sixteen miles east of Los Angeles. In the foothills of the Sierra Madre Mountains, at an elevation of 1600 feet. On the main line of Santa Fe Railway. Connected with Los Angeles by interurban railway and splendid boulevards.

ENVIRONS

The grounds consist of a beautiful park of forty acres, in which are found a variety of native Live Oaks, subtropical trees and plants, and a profusion of beautiful shrubs and flowers. Many winding walks and nooks of exquisite beauty add to its attractiveness. When on exercise, patients also enjoy the beautiful trails in the adjoining canyons and mountains.

MEDICAL CARE

Competent resident staff. Examinations for comparison every six weeks. Close medical supervision. Individual needs and problems receive personal attention.

THERAPEUTIC CARE

Fads are not followed, but an endeavor is made to give patients the amount of rest and exercise suited to their individual needs; the benefits of a liberal and adequate diet; such tonic measures as will increase their resistance, and other measures that will help them overcome any disturbing symptoms or complications that may arise. Heliotherapy, tuberculin, pneumothorax and surgery employed whenever indicated.

Weekly rates from \$25.00 up, including medical attention, medicines (except expensive remedies) and general nursing. Extra charge for operative measures (except pneumothorax).

DIAGNOSTIC CLINIC

A diagnostic clinic is maintained for the study of all diseases of the chest.

E. M. POTTENGER, M.D., Medical Director

1 - Pottenger Allen

THE POTTENGER SANATORIUM, Monrovia, California

THE ANALYSIS SHOWS

THE VALUABLE ALKALINE CHARACTER OF

VICHY CÉLESTINS

Natural Mineral Water

INDICATIONS

In stomach and
liver affections
and digestive disorders
in general;
in gout, arthritis
associated with uric
acidemia, uricemia,
and nephrolithiasis of
uric acid origin.



BOTTLED
AT THE SPRING
VICHY, FRANCE

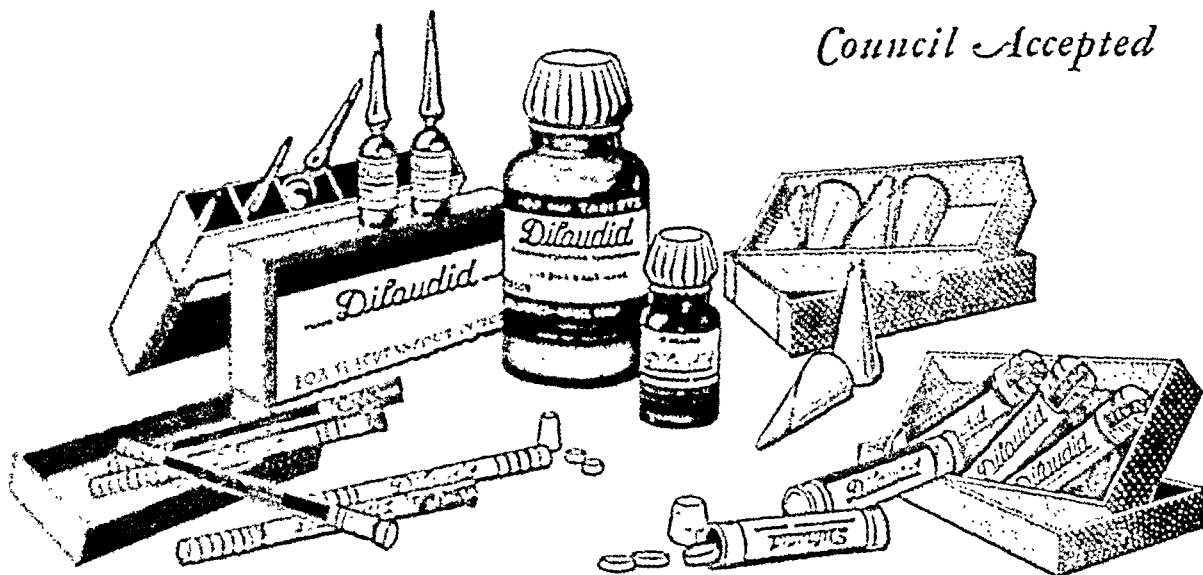
ANALYSIS (GRAMS PER LITER)

Sodium bicarbonate	3.3090
Potassium bicarbonate	0.2490
Lithium bicarbonate	0.0281
Calcium bicarbonate	0.7400
Magnesium bicarbonate	0.1016
Ferrous bicarbonate	0.0012
Sodium chloride	0.3830
Sodium sulphate	0.2430
Silica	0.0300
Sodium arseniate, Phosphate and nitrate	} present

Brochure with Therapeutic Data and Medical Bibliography
sent on request.

Sole United States Agents, American Agency of French Vichy, Inc., 503 Fifth Ave., New York

Council Accepted



Dilaudid

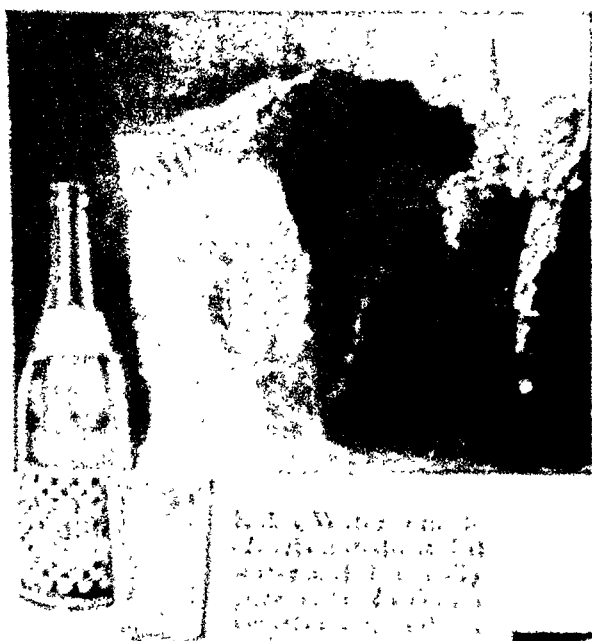
*An advance in opiate medication
for relief of pain and cough*

For a trial quantity send your Federal Narcotic order for 1 x 20 H.T. 1/20 gr. or 1 x 10 O.T. 1/20 gr. Dilaudid

MANUFACTURED IN U.S.A.

BILHUBER-KNOLL CORP., 154 Ogden Ave., JERSEY CITY, N. J.

A Pure, Palatable, Carbonated PREPARED WATER



THERE are many conditions, no doubt, where you will want your patient to increase his daily intake of water.

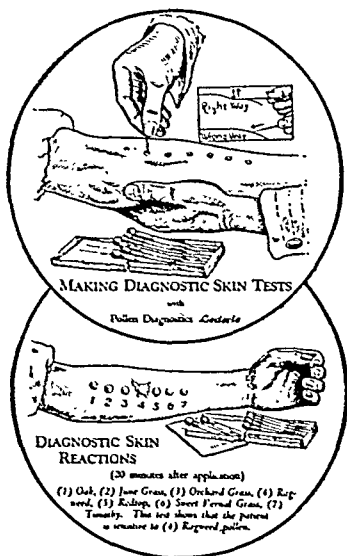
In such cases, why not suggest the use of Kalak Water, the palatable, carbonated alkaline water prescribed by physicians for over twenty years.

Kalak

For **20** Years

HAY FEVER *has been prevented* *in thousands of cases* **Pollen Antigen** *with* **Lederle**

INTRODUCED BY LEDERLE LABORATORIES IN 1914



DIAGNOSIS OF HAY FEVER

With the Lederle Diagnostic Pollen Tests the diagnosis may be made in your office or in the patient's home. A positive reaction occurring with a pollen to which the patient is known to be exposed when he is having Hay Fever indicates the Pollen Antigen to be used in desensitizing the patient. The test is easily performed, accurate and safe.

**For Hay-Fever occurring from
August 1st to Frost**

If the diagnostic skin reactions from both species of ragweed are about equal in size and larger than reactions produced by other pollens, and provided the history of the case shows that the person's hay-fever symptoms occur from August 1st to frost, use **Pollen Antigen Lederle, Ragweed Combined**.

Literature upon request

LEDERLE LABORATORIES Incorporated
511 FIFTH AVENUE, NEW YORK

Calcium Deficiencies IN TETANY

"WHEN all the facts of tetany are arrayed it is impossible to escape the impression that there is a fundamental relation between the various types," is the opinion of Peters and Van Slyke.¹

The disorder may take such forms as the spasmodophilia of infancy, the tetany of pregnancy, the convulsions of uremia, postoperative tetany, parathyroid tetany, and that associated with osteomalacia.

Cantarow² finds that when serum calcium falls below 7 mg. per 100 c.c. symptoms of tetany are manifest.

Alfred Hess notes that tetany occurs "frequently, in fact generally, in a latent form."³ In view of this the physician must be on guard against tetany in those cases where there is likely to be a drain on the calcium store, particularly during growth and in pregnancy and lactation. Considering that the average diet is probably lower in calcium than in any other chemical

element, the problem of increasing calcium intake through ordinary foods is difficult. Calcium salts, moreover, are not usually relished by the patient.

A larger intake of calcium alone is not effective, however, unless the body is able to utilize the added minerals. Moreover, tetany is marked by elevations of serum phosphorus, according to Collip.⁴ Thus the problem arises not only of increasing calcium concentration but also of maintaining the proper ratio between calcium and phosphorus. "Vitamin D, as is well known, has remarkable power to regulate calcium and phosphorus metabolism," McCollum observes.⁵

Alfred Hess declares increased calcium intake together with viosterol to be the treatment of choice in tetany.³ He adds the significant comment that in tetany viosterol is characterized by its rapid action, whereas cod liver oil, in infantile tetany at least, appears to act upon the concomitant ricketic condition rather than upon the tetany.

MEAD'S CEREAL

Enriched with cereal and other calcium foods

SUPPLIES Calcium

Containing 0.22 Gm. Ca and 0.17 Gm. P per ounce, this delicious cereal is richer in these minerals than most principal breakfast cereals. It supplies as much calcium as 12 ounces of fluid milk, and thus covers the need for excessive quantities of liquid in the diet. It also contains 100% of iron and vitamins B1 and B2 of milk.

¹⁻⁵ Bibliographies on request.

MEAD'S VIOSTEROL

IN OIL 250 D

UTILIZES Calcium

Alfred Hess says of viosterol: "One of the distinctive characteristics of this remarkable substance is that it raises the level of either inorganic phosphorus or of calcium, depending on which is in low concentration in the blood or tissues."⁶ Infinitely potent, accurately measured, Mead's Viosterol can be depended upon for good results in tetany.

MEAD JOHNSON & CO., Evansville, Ind., Pioneers in Vitamin Research

For more information on the importance of calcium in the diet, or for a list of dealers, write to Mead Johnson & Co., Evansville, Ind., or to your nearest drug store.

© 1934 Mead Johnson & Co., Evansville, Ind.

ANNALS OF INTERNAL MEDICINE

VOLUME 7

JUNE, 1934

NUMBER 12

TREATMENT OF ANGINA PECTORIS AND CONGESTIVE HEART FAILURE BY TOTAL ABLATION OF THE THYROID IN PATIENTS WITHOUT THYROTOXICOSIS

X. WITH PARTICULAR REFERENCE TO THE PRE- AND POST-OPERATIVE MEDICAL MANAGEMENT *

By H. L. BLUMGART, D. D. BERLIN, DAVID DAVIS, J. E. F. RISEMAN and
A. A. WEINSTEIN, *Boston, Massachusetts*

IN the treatment of patients with congestive failure and angina pectoris, one not infrequently finds that despite all available medical measures the patients, while improved, nevertheless continue to remain chronically incapacitated. It is well recognized that exercise, emotion and other factors which increase cardiac work tend to increase congestive heart failure and angina pectoris. The enforcement of diminished activity or complete bed rest benefits patients by reducing the demands on the heart. The use of sedatives and the action of digitalis in reducing the ventricular rate in auricular fibrillation have a similar effect.^{3, 10, 27}

The same considerations underlie the treatment of thyrotoxic heart disease.^{22, 23} It has long been known that in thyrotoxicosis subtotal thyroidectomy usually accomplishes permanent lowering of the basal metabolic rate from abnormally high levels to a normal level, with coincident improvement in congestive failure^{15, 16, 17, 18} or angina pectoris^{19, 20} as the demands on the heart are lessened.⁴ Conversely, patients with spontaneous myxedema not infrequently develop angina pectoris or the signs and symptoms of congestive failure because of the increased demands on the heart when thyroid is administered.^{5, 8, 21, 24}

We have attempted to extend this therapeutic principle of diminution in cardiac work by still further lessening the demands on the heart in patients with intractable heart disease. This has been done by purposefully inducing the low metabolic rate of hypothyroidism through total ablation of the thyroid gland. Subtotal removal of the normal thyroid gland does not assure persistent lowering of the basal metabolic rate from

* Read before the American College of Physicians, Chicago, April 17, 1934.

From the Medical Service and Research Laboratories of the Beth Israel Hospital, and the Department of Medicine, Harvard Medical School, Boston.

This investigation was aided by a grant from the William W. Wellington Memorial Research Fund of the Harvard Medical School, Boston.

normal levels to subnormal levels.^{2,6} Maximal subtotal removal of the normal gland may occasionally induce persistent hypothyroidism, but many patients will not show a permanent reduction in metabolic rate. In such instances, subsequent surgical attempts to remove residual fragments have been unsuccessful; nor have the residual fragments of gland been affected by heavy roentgen-ray radiation to the point of dermatitis.^{2,12} In brief, our work has demonstrated that nothing short of complete removal of every vestige of thyroid tissue can assure the production of persistent hypothyroidism.

In a series of 60 patients with intractable heart disease, we have removed the entire normal thyroid gland with results that are encouraging. Most of these patients were chronic invalids, having suffered from congestive heart failure or angina pectoris, which was unrelieved in spite of the employment of all available therapeutic measures over a period of years. The condition of all these patients was such that any significant improvement could be definitely attributed to the operative procedure. Of the 40 patients with congestive heart failure due to various etiologies, over half the patients have been economically rehabilitated and have been able to resume light or moderately heavy work. These patients have shown no recurrence of signs or symptoms of failure over a period of three to 16 months, in spite of such activity. They are still handicapped individuals in that they are probably not able to undertake heavy manual labor. In the 16 months that have elapsed since the first operation was performed, five patients have suffered temporary recurrent cardiac failure, in three of whom it was due to the omission of digitalis, over exertion, or recurrence of bronchial asthma.

In the 20 patients with angina pectoris, attacks of pain were experienced repeatedly, either at rest or on relatively moderate exertion before operation. Ten patients have had no recurrence of attacks since operation. Of the remaining ten patients, seven have shown capacity to perform two to three times as much work as preoperatively before experiencing pain, and three patients have shown but little clinical improvement.

In the series of 60 patients, there have been six postoperative deaths, a mortality rate of 10 per cent. It should be noted that all deaths occurred in patients with advanced congestive failure and were all due to postoperative pulmonary complications. It should also be noted that these six deaths occurred in the first 40 operations that were performed. In the last 20 patients, who were as severely incapacitated as the first group of 40, there have been no deaths. Of the patients with congestive failure, five have died since operation, at intervals of eight and 12 months respectively after operation. Two died of pneumonia, one after alcoholism and one after a fall. Of the patients with angina pectoris, one died of a myocardial infarction, one of a cerebral embolism, and one of congestive heart failure. The patient who died of congestive heart failure died during the operation. The patient who died of a cerebral embolism died in the postoperative period. The patient who died of a myocardial infarction died in the postoperative period.

on over a year ago is most encouraging in that more than half have been able to maintain the degree of benefit conferred by the operation without evidence of recurrence of failure or of any encroachment on their cardiac reserve.

SELECTION OF PATIENTS

The criteria for the proper selection of patients can be established only after the results have been observed over a period of years in numerous patients, representing the various forms and degrees of severity of cardiovascular disease. Although we have operated on 60 patients with cardiovascular disease during the past 16 months, the number is small from a statistical point of view and the elapsed postoperative interval too brief to permit the deduction of final conclusions. It may, however, be of value to state our tentative opinion at the present time.

The use of a therapeutic procedure as radical as this should be reserved at the present time, we feel, for those patients who in spite of all available therapeutic measures remain cardiac invalids. Only after prolonged and adequate medical treatment has failed to relieve the patient should the operation be considered. Before the operative procedure is undertaken, the patient's condition should be improved to the fullest possible extent so that the operative risk is minimal. Patients should not be operated on until the signs and symptoms of acute congestive failure have disappeared at complete rest in bed. Patients who gain edema in spite of prolonged rest in bed are poor candidates for operation, although a few of our most striking results have occurred in such patients. The presence of pulmonary congestion predisposes to postoperative bronchopneumonia, and most of our postoperative deaths have occurred in this group. In considering a procedure of this type, the clinician may be tempted to operate on a patient with congestive failure who is rapidly becoming worse in a desperate effort to do something for the patient. This must be avoided, for such patients will obviously not withstand the operative procedure. Patients who, in spite of medical treatment, have suffered from recurrent failure on exertion over a considerable period, but whose condition is only slowly progressive, are favorable subjects.

There is no reason to believe that the induction of hypothyroidism by the complete removal of the gland will retard the development of arteriosclerosis or impede the narrowing of the valvular orifices or retard active syphilitic aortitis. One should expect that, although patients who show a rapidly progressive preoperative clinical course may experience temporary and perhaps considerable improvement, they will probably succumb to the underlying disease process sooner than other patients with a less rapidly progressing condition. For this reason, we have not operated on patients with malignant hypertension, and have accepted only occasional cases with luetic heart disease. Similarly, patients with rheumatic or arteriosclerotic heart disease who have given a short but progressive history of failure are unfavorable candidates.

Since the effect of total thyroidectomy on the immune reactions in acute infections is unknown, the presence of active rheumatic involvement contraindicates the operation at present. It would, moreover, be difficult to judge whether improvement in such patients was due to the cessation of active infection or the results of thyroidectomy. Similarly, patients with pulmonary infection, such as bronchiectasis, are much more likely to develop bronchopneumonia during or after operation. Patients with recent coronary thrombosis are of course poor operative risks. Seven of our patients had a history of one to three previous attacks of coronary thrombosis, but in every instance the last attack had occurred at least four months before operation. The presence of renal insufficiency contraindicates the procedure.

Our experience indicates that a basal metabolic rate of less than minus 15 per cent before operation is an unfavorable factor, and a basal metabolic rate lower than minus 20 per cent probably contraindicates the operative procedure. Our experience shows that when the basal metabolic rate reaches a level of about minus 30 per cent small doses of thyroid are indicated in order to obviate the development of fatiguability, puffiness of the face, mental slowing and other distressing symptoms and signs of myxedema. In accord with our previous studies,^{3,6,7} patients who showed a basal metabolic rate of minus 20 per cent before operation therefore experienced but slight cardiac improvement before their basal metabolic rate dropped to about minus 30 per cent, the level at which the symptoms of myxedema necessitated the administration of thyroid. Our clinical results have been in accord with these considerations, for of the six patients who have shown but little improvement, four showed low preoperative metabolic rates.

Insofar as the extent of duration of improvement after operation depends in large part on the degree of preexisting cardiac pathology and the residual functional capacity of the heart, patients must not expect to be able to go back to strenuous activity. If they are bedridden with congestive failure or angina pectoris, they probably will enjoy freedom from failure or pain when up and about. If before operation they become decompensated and develop angina only on mild exertion, they will enjoy a moderate increase in activity. If preoperatively they develop congestive failure or angina only on moderate exertion, they will probably be able to do productive work without the development of such signs and symptoms.

In order to help to make our present conception of a hypothetical case more concrete, let us consider a very favorable candidate for thyroidectomy. The patient would be between 20 and 50 years of age with a history of rheumatic fever at least 10 years and a basal metabolic rate of minus 20 per cent or lower. He has a moderate to severe mitral regurgitation, moderate aortic regurgitation, and a history of coronary thrombosis. The hypothetical patient is a married, middle-aged person from whom the removal of the thyroid gland would be expected to free him of the symptoms of myxedema, to improve his cardiac condition, and to protect him from the

hospital treatment. His condition has not become rapidly worse but he is incapacitated. He always regains circulatory compensation after resting in bed for several weeks, indicating that he still has some cardiac reserve. His condition does not permit him, however, to undertake normal activities. Since he becomes edema free at rest, the risk of operation is slight. Since he has not shown a rapidly progressive downhill course, his prognosis after thyroidectomy is good. He will probably be able to lead a definitely more active life than before, without becoming decompensated. The hypothetical patient with angina pectoris has attacks on slight exertion but not at rest and does not show any of the unfavorable factors mentioned above. He will probably be completely free of attacks after operation, or develop attacks only after moderately severe exertion.

PREOPERATIVE MANAGEMENT

We have treated our patients with all available medical measures preoperatively until they showed no further improvement in order that their condition might be as favorable as possible before operation and the risk of operation be reduced to a minimum.⁷ All our patients are at best fragile operative risks and cannot withstand the complications that other more normal subjects might easily surmount. Before operation all patients have been kept at complete rest in the hospital for several weeks to several months, depending upon the signs and symptoms of failure and the length of time spent at rest prior to entry. Patients who suffer from pulmonary congestion in spite of prolonged rest and show cyanosis may be benefited by oxygen therapy. Dr. Alvan Barach of New York informs us that he has found this adjunct in therapy particularly helpful in his patients.¹ In patients with auricular fibrillation, somewhat greater doses of digitalis are necessary before operation than are usually employed in order that the ventricular rate shall be adequately controlled during the course of the operation. Medicines which we intend to use during the operative or postoperative course are always administered days or weeks before operation and their effects observed. Morphine has been administered to each patient some days before operation in order to be certain that no hypersensitivity or idiosyncrasy exists. In some patients in whom such a state has existed, we have resorted to other drugs. Patients usually receive one of the barbituric acid derivatives the night before operation, and again early on the day of operation. It is advisable to give sufficient preoperative sedation to produce drowsiness; narcosis, however, is to be avoided. If patients are still alert or nervous immediately before operation, $\frac{1}{6}$ or $\frac{1}{4}$ grain of morphine is injected subcutaneously.

OPERATIVE COURSE

All operations are now performed under local anesthesia. Patients with congestive failure are placed almost in the orthopneic position on the operating table to avoid respiratory embarrassment and to collapse distended veins in the operating field. A medical advisor is present at all operations

to follow the reaction of the patients to operation. If necessary, the operation is terminated at his suggestion. One lobe of the thyroid is removed and direct laryngoscopy is then performed by Dr. Louis M. Freedman.¹¹ If the recurrent laryngeal nerve on the side of operation has been injured and the vocal cord on that side has been paralyzed, the operation is terminated, obviating the danger of bilateral vocal cord paralysis. In only two instances has interruption of the operation been necessary. In both of these cases the function of the vocal cord returned to normal and the other lobe was subsequently removed. The surgical precautions to be observed are of the greatest importance. Total thyroidectomy presents surgical difficulties in relation to the recurrent laryngeal nerves and the parathyroid glands, not inherent in the usual subtotal thyroidectomy. These problems have been fully discussed elsewhere by Dr. David D. Berlin, who has been in charge of the surgical aspects of this work.^{7, 8, 7}

POSTOPERATIVE MANAGEMENT

Patients who undergo the operation according to the above régime have shown but slight postoperative reaction. Experience has shown that postoperative complications are minimized if sedatives are administered as sparingly as is consistent with maintaining the patient comfortable. Patients are awake immediately after operation and raise accumulated bronchial secretions, thereby reducing the danger of postoperative bronchopneumonia to a minimum. Fluids can be taken by mouth immediately after operation, thereby obviating the discomfort of hypodermoclysis. In patients with peridontal edema, fluids and salt are of course restricted, and oxygen therapy is frequently employed immediately after operation. These patients are followed closely by a medical intern, following the suggestions of the medical staff. Special day and night nurses are employed who are familiar with the care of the patients and are trained to recognize early signs of respiratory distress and parathyroid insufficiency. Parathyroid tetany in the sense of Crumbiehl,¹² etc., has never occurred in our cases.¹³ Between the first and fourth postoperative day 12 patients have shown numbness and tingling in various parts of the body, positive Trousseau and positive Chvostek signs. These manifestations of latent tetany have been satisfactorily controlled by the subcutaneous injection of 4 to 10 c.c. of 55 per cent calcium chloride solution, four or five times; an initial dose of 10 to 20 c.c. of 10 per cent calcium chloride solution intravenously in certain cases when an immediate response was desired. If calcium chloride is not well tolerated by the patient, 5 to 10 c.c. of 10 per cent calcium gluconate may be employed. The subcutaneous injection is most useful in the control of signs in preventing additional signs. The intravenous injection is useful in relieving all remaining symptoms. The patient is kept on a liquid diet for 24 hours after the operation. The patient is then transferred to a ward of a hospital, leaving hospital from the ward on the second or third day.¹⁴ The importance of a carefully planned postoperative management is emphasized by the following case which is presented

immediately after operation, experience indicates that complete bed rest should be enforced until the basal metabolic rate has shown a significant lowering of approximately 20 per cent from its preoperative level. Rest in bed for three or four weeks after operation is usually advisable. Activity should be increased only gradually during the following weeks.

In all patients, persistent hypothyroidism has intervened. The extent of permanent relief has in general been related to the degree of reduction in the basal metabolic rate.⁷ With a lowering of the basal metabolic rate, patients show what may be termed the mild symptoms and signs of myxedema, which consist of increased sensitivity to cold, somewhat thickened and dry skin, and slow growth of hair. With basal metabolic rates of minus 30 per cent or lower, most patients suffer from puffiness of the face, weakness of the legs, and irritability. By the administration of small doses of thyroid, the basal metabolic rate can be successfully maintained at a level of minus 25 to minus 30 per cent, which frees the patient from the untoward symptoms of myxedema, but which nevertheless decreases the burden on the heart. The optimum metabolic rate level for each patient varies somewhat but is usually between minus 25 and minus 30 per cent. One-fourth grain thyroid is usually sufficient to maintain this level, but in some patients only $\frac{1}{8}$ grain is necessary, while in others $\frac{1}{2}$ grain is needed.^{9, 14} The optimum dose of thyroid must be ascertained in each patient on the basis of the clinical signs and symptoms of hypothyroidism, basal metabolic rate measurements, and, at times, determination of the serum cholesterol concentration.¹⁴ All patients should be seen at least once a month for it is entirely unnecessary for a patient to suffer from the distressing symptoms of myxedema.

Throughout their lives these patients should receive the same close medical observation and treatment that all cardiac patients require. The management of the cardiac condition is usually the same as before the operation as regards drugs, although in a few patients with auricular fibrillation it has seemed that slightly less digitalis is necessary. Most patients feel so much better that they must be warned not to overdo. Operation does not alter the underlying pathological process, and so it is important that they should not overtax themselves. Some of our patients because of their economic situation are working 12 to 16 hours a day, and one patient who previously suffered from angina pectoris has been working as a day laborer for over six months. This is clearly inadvisable. A few patients who similarly have been forced to work strenuously have had temporary recurrence of congestive failure or angina pectoris. Other patients have their previous sufferings so vividly before them that they must be encouraged to undertake effort. The fear of recurrence of angina pectoris or congestive failure presents a serious psychological problem in some patients.

The social-economic problems in our patients have been many. Some of our young patients have been invalided since adolescence and have had

to be taught an occupation. Others, while unable to undertake the heavy work of their occupation before they were invalided, have been able to secure employment demanding less strenuous effort. These considerations are exemplified by the first patient, a chef, in whom the entire thyroid gland was removed on December 15, 1932. He suffered from angina pectoris and congestive heart failure and had been confined to bed for over two years. Edema of the legs appeared if he was up and about for even a few hours and was accompanied by substernal pain radiating to the left scapula and left arm, relieved only temporarily by nitroglycerine. He has been unable to go back to his previous occupation, but is able to carry on as a porter in our laboratories, doing light work eight hours daily. If he attempts to increase his activity by moving beds or lifting heavy objects, he experiences pain over his scapula which subsides immediately on cessation of effort.

The final appraisal of this new therapeutic procedure awaits the results attained in numerous patients with various types of cardiovascular disease. Whether the duration of life is actually prolonged by this treatment can only be ascertained by studying the subsequent history of these patients over a longer period of time. At present we may state, however, that we have been able to prolong the useful and comfortable life of most of our patients since they were almost all incapacitated before operation. The results are encouraging and the operation should be considered in patients who are incapacitated and who conform to the considerations outlined in this communication.

BIBLIOGRAPHY

1. BARACH, A.: Personal communication.
2. BERLIN, D. D.: Therapeutic effect of thyroidectomy on congestive heart failure and angina pectoris in patients with no clinical or pathological evidence of thyroid toxicity; operative technic, *Am. Jr. Surg.*, 1933, xxi, 173-179.
3. BLUMGART, H. L.: Velocity of blood flow in health and disease, *Medicine*, 1931, x, 1-75.
4. BLUMGART, H. L., GARGILL, S. L., and GILLIGAN, D. R.: Studies on velocity of blood flow; circulatory response to thyrotoxicosis, *Jr. Clin. Invest.*, 1930, ix, 69-89.
5. BLUMGART, H. L., GARGILL, S. L., and GILLIGAN, D. R.: Studies on velocity of blood flow; circulation in myxedema, with comparison of velocity of blood flow in myxedema and thyrotoxicosis, *Jr. Clin. Invest.*, 1930, ix, 91-106.
6. BLUMGART, H. L., LEVINE, S. A., and BERLIN, D. D.: Congestive heart failure and angina pectoris; therapeutic effect of thyroidectomy on patients without clinical or pathologic evidence of thyroid toxicity, *Arch. Int. Med.*, 1933, li, 866-877.
7. BLUMGART, H. L., RISEMAN, J. E. F., DAVIS, D., and BERLIN, D. D.: Therapeutic effect of total ablation of normal thyroid on congestive heart failure and angina pectoris; preliminary results in various types of cardiovascular disease and coincident pathologic states without clinical or pathologic evidence of thyroid toxicity, *Arch. Int. Med.*, 1933, lii, 165-225.
8. CHRISTIAN, H. A.: Heart and its management in myxedema, *Rhode Island Med. Jr.*, 1925, viii, 109-118.
9. DAVIS, D., WEINSTEIN, A. A., RISEMAN, J. E. F., and BLUMGART, H. L.: Treatment of chronic heart disease by total ablation of the thyroid gland. VII. The heart in artificial myxedema, *Am. Heart Jr.* (To be published.)

10. DuBois, E. F.: Total energy exchange in relation to clinical medicine, *Bull. N. Y. Acad. Med.*, 1933, ix, 680-693.
11. FREEDMAN, L. M.: Treatment of angina pectoris and congestive heart failure by total ablation of the thyroid. V. Importance of laryngoscopic examination as a means of preventing bilateral paralysis of the vocal cords, *Arch. Otolaryng.*, 1934, xix, 383-386.
12. FRIEDMAN, H. F., and BLUMGART, H. L.: Treatment of chronic heart disease by lowering the metabolic rate. The necessity for total ablation of the thyroid, *Jr. Am. Med. Assoc.*, 1934, cii, 17-21.
13. GILLIGAN, D. R., BERLIN, D. D., VOLK, M. C., STERN, B., and BLUMGART, H. L.: Therapeutic effect of total ablation of normal thyroid on congestive heart failure and angina pectoris. IX. Postoperative parathyroid function. Clinical observations, and serum calcium and phosphorus studies. (To be published.)
14. GILLIGAN, D. R., VOLK, M. C., DAVIS, D., and BLUMGART, H. L.: Therapeutic effect of total ablation of normal thyroid on congestive heart failure and angina pectoris. VIII. The relationship between the serum cholesterol, the basal metabolic rate and the clinical aspects of hypothyroidism, *Arch. Int. Med.* (To be published.)
15. HAMILTON, B. E.: Hearts in hyperthyroidism, *Boston Med. and Surg. Jr.*, 1922, clxxxvi, 216-218.
16. HAMILTON, B. E.: Thyroidism complicated by heart failure, *Jr. Am. Med. Assoc.*, 1923, lxxx, 1771-1774.
17. HAMILTON, B. E.: Heart failure of congestive type caused by hyperthyroidism, *Jr. Am. Med. Assoc.*, 1924, lxxxiii, 405-410.
18. LAHEY, F. H., and HAMILTON, B. E.: Thyrocardiacs; their diagnostic difficulties; their surgical treatment, *Surg., Gynec. and Obst.*, 1924, xxxix, 10-14.
19. LEV, M. W., and HAMBURGER, W. W.: Association of angina pectoris and hyperthyroidism, *Am. Heart Jr.*, 1928, iii, 672-681.
20. LEV, M. W., and HAMBURGER, W. W.: Studies in thyroid heart disease; angina pectoris and hyperthyroidism, *Am. Heart Jr.*, 1932, viii, 109-113.
21. MACKENZIE, J.: Angina pectoris, Oxford Medical Publications, 1923, H. Frowde, London.
22. MEANS, J. H.: Address on certain aspects of pathogenesis of angina pectoris, *Canad. Med. Assoc. Jr.*, 1931, xxiv, 193-200.
23. MEANS, J. H., and RICHARDSON, E. P.: The diagnosis and treatment of diseases of the thyroid; in CHRISTIAN, H. A.: Oxford monographs on diagnosis and treatment, vol. 4, 1929, Oxford University Press, New York.
24. MEANS, J. H., WHITE, P. D., and KRANTZ, C. I.: Heart in myxedema, with special reference to dilatation and angina pectoris, *Boston Med. and Surg. Jr.*, 1926, cxcv, 455-460.
25. RISEMAN, J. E. F., and STERN, B.: A standardized exercise tolerance test for patients with angina pectoris on exertion. (To be published.)
26. WEINSTEIN, A. A., DAVIS, D., BERLIN, D. D., and BLUMGART, H. L.: Observations on the mechanism of the early relief of pain in patients with angina pectoris and congestive failure after total ablation of the normal thyroid gland, *Am. Jr. Med. Sci.* (In press.)
27. WEISS, S., and BLUMGART, H. L.: Effect of digitalis bodies on velocity of blood flow through lungs and on other aspects of circulation; study of normal subjects and patients with cardiovascular disease, *Jr. Clin. Invest.*, 1929, vii, 11-26.

A STATISTICAL EVALUATION OF DIFFERENT METHODS FOR THE DETECTION OF ARTERIOSCLEROSIS IN DIABETES MELLITUS *

By I. M. RABINOWITCH, F.A.C.P., W. L. RITCHIE, and S. HANFORD
McKEE, *Montreal, Canada*

THE purpose of this paper is to report the results of a statistical evaluation of different methods for the detection of arteriosclerosis in diabetes mellitus. This investigation was prompted by the high and increasing incidence of vascular disease among diabetics and its influence upon mortality.

In spite of control of coma and of tuberculosis—the two major causes of death among diabetics in the past—the death rate from diabetes mellitus in large populations is still high; and mortality and morbidity data clearly indicate that cardio-vascular disease is one of the most important contributing factors. In table 1, are recorded cardiovascular conditions and their incidences among 1500 diabetics in the Clinic for Diabetes at The Montreal General Hospital.

TABLE I
Cardio-Vascular Conditions among 1500 Diabetics in the Clinic for Diabetes at the Montreal General Hospital

Condition	Number	Average Age (years)
Angina pectoris.....	19	58.5
Cataract.....	85	61.3
Cerebral arteriosclerosis.....	14	60.5
Cerebral hemorrhage.....	13	60.4
Cerebral spasm.....	12	56.0
Cerebral thrombosis.....	18	61.7
Coronary thrombosis.....	7	55.8
Gangrene.....	118	61.5
Hypertension.....	249	56.3
Intermittent claudication.....	4	54.0
Myocarditis.....	50	59.4
Pre-uremia.....	2	62.5
Uremia.....	7	55.0

The above do not include all of the cardio-vascular disturbances. In some cases, for example, the only evidence of arteriosclerosis was calcification of the arteries of the lower extremities. The arterial changes had produced no symptoms; and aside from the diabetes, these individuals were healthy. The calcifications were discovered accidentally because of our routine roentgenological examination.

Attention is drawn particularly to the high incidence of hypertension, namely, 16.6 per cent. Prior to the discovery of insulin, increased blood

* Received for publication April 3, 1934.

From the Departments of Metabolism, Roentgenology and Ophthalmology, The Montreal General Hospital, Montreal, Canada.

pressure was not prominent among diabetics. This was to be expected, since the average duration of life from the onset of the diabetes was but a few years. Neither Elliott¹ nor Janeway² was impressed with the importance of this association. With better control of the diabetes by diet and insulin, conditions have changed. The diabetic now lives long enough to develop cardio-vascular disease.

Whether hypertension should be regarded as a clinical entity, independent of vascular disease, or whether it should be considered as a manifestation of vascular disease, is, for the purpose of this investigation, irrelevant; it is of academic interest only. Of practical importance is the fact that, when selected at random, more diabetics have hypertension than a similarly selected group of nondiabetics. That hypertension may lead to arteriosclerosis is a well recognized fact. Therefore, if hypertension is common among diabetics, in spite of control of the diabetes, and commonly leads to vascular disease, it may be properly included in this study; the relationship may be regarded as causal and not accidental.

The above incidence of vascular disease, though obviously high, would appear to be gratifying; as stated, the diabetic now lives long enough to develop these conditions, whereas in the past, death from coma and tuberculosis prevented him from doing so. The disturbing feature, however, is age. In table 1 are recorded the average ages for the corresponding conditions; and these appear to be satisfactory. Averages, however, require interpretation. One of the theorems of statistics tells us that the *arithmetical mean* of a large series of observed values is the most probable value of the quantity measured.* It should, therefore, be noted that, with very few exceptions, the above averages have been calculated from a small number of cases. Under such conditions, the *mean* is not necessarily the same as the *mode* or typical value; a few extremely high or low values could appreciably influence the *mean*, and this was found to be so. While tabulating the data we were repeatedly impressed with the young ages: angina pectoris at the age of 39 years, cerebral hemorrhage at 41 years, cerebral spasm at 37 years, cerebral thrombosis at 43 years, coronary thrombosis at 39 years; hypertension at 34 years, advanced cerebral arteriosclerosis at 37 years, marked retinitis at 47 years, cataract at 18 years, and arteriosclerosis at 12 years. At present, death from arteriosclerosis is rare among juvenile diabetics. The death rate from all causes is low among diabetic children. This, however, is no indication of ultimate prognosis. It may here be observed that life assurance companies do not accept arteriosclerotics as standard risks. Children with arteriosclerosis are no exception. Regardless of age, the expectation of life of the arteriosclerotic is definitely less than the normal.

We are not alone in these experiences. Among a group of 50 diabetics under 40 years of age in Dr. Joslin's clinic, Shepardson³ found that 18, an incidence of 36 per cent, had vascular sclerosis, according to roentgen-ray

* This holds only when the frequency distribution is symmetrical.

examination. Wilder⁴ noted a high postmortem incidence of arteriosclerosis among diabetics under 40 years of age and Shields Warren's experiences are particularly worthy of note here. In table 26 of his book on "The Pathology of Diabetes Mellitus"⁵ Warren records the findings in 264 autopsies upon diabetics. Of these 264 cases, there were 72 individuals of 40 years of age or under; and of these 72 individuals, 36 (an incidence of 50 per cent) had tissue changes secondary to arteriosclerosis. In one case, death was due directly to arteriosclerosis.

Is the incidence of arteriosclerosis increasing and, if so, is the increase more apparent than real? An apparent increase is to be expected, since other important causes of death have been greatly reduced. A little over a decade ago, coma was the chief cause of death among diabetics. This condition is rapidly disappearing; in 1933 in the Clinic for Diabetes at The Montreal General Hospital there were three cases only. That this was not accidental is shown by the small number of such cases in the immediately preceding years; in 1932, there were five; in 1931 there were five, and in 1930 there were six.

Apparent or real, the incidence of arteriosclerosis is very high. It is appreciably affecting mortality among adults and, if not controlled, must sooner or later exert the same effect among children. Control of diabetes is generally judged by the control of hyperglycemia, glycosuria and nutrition, that is, by blood and urinary sugar, body weight and activity of the individual. In view of the possibility of premature death from arteriosclerosis, it is obvious that these criteria alone do not afford a true index of progress; and it may here be observed that it affords very little comfort to know that, in a person who died of a cerebral hemorrhage or heart failure, the diabetes, at the time of death, was under ideal control; that the urine was free of sugar and acetone bodies and the blood sugar was normal. Relatives are concerned with the death and not with its cause.

Further disturbing is the fact that in the majority of these diabetics with cardio-vascular-renal disease the diabetes was mild. This emphasizes a well recognized fact, namely, that cardio-vascular or cardio-vascular-renal disease is not related to the severity, but to the duration of the diabetes. (Children are no exception to this rule.) Most of our patients with angina pectoris, coronary thrombosis, cerebral hemorrhage, hypertension, heart failure, etc. have mild diabetes; the urine is readily freed and kept free of sugar and acetone bodies and the blood sugar is kept normal or nearly so with diet alone. Relatively few of these patients require insulin.

An important problem in the management of the diabetic is, therefore, clear. If the expectation of life of the diabetic is to approach that of the normal individual, premature arteriosclerosis must be prevented and, if present, must be controlled. Prevention and control depend upon recognition of cause, early detection and appropriate treatment.

In the present article we are presenting data which bear upon the question of the diagnosis of arteriosclerosis. An attempt was made to evaluate the

relative sensitivities of a number of well recognized procedures: namely, ordinary clinical examination, examination of the ocular vessels (fundus), roentgenological examination of the legs and feet for calcification of vessels, and roentgenological estimation of the size of the heart.

CLINICAL METHODS

In many cases, clinical examination alone suffices. With such conditions as cerebral hemorrhage, gangrene, coronary thrombosis, etc., vascular disease is obvious. In all such conditions, however, the pathological changes are well advanced. The difficult problem is early diagnosis.

There are the four suggestive signs of arteriosclerosis, namely, (a) thickened radial vessels, (b) hypertension, (c) enlargement of the heart, and (d) accentuation of the aortic second sound. These, when found together, form a picture which is pathognomonic. Singly, however, they have their limitations. Palpation of the arteries is a common clinical procedure and attempts have often been made to estimate the degree of arteriosclerosis by this simple process. The practice is old, but, to quote Shields Warren⁵ it is as old as it is uncertain. It is, for example, very difficult at times to distinguish between thickness due to arteriosclerosis and a palpable artery due to hypertension. In either case, the findings at least suggest disease. The chief difficulty is interpretation of normal thickness and normal tension; it does not necessarily follow that an artery, normal according to palpation, is normal; calcification may be quite marked.

Estimation of the size of the heart may be misleading, because of the many vagaries of percussion. It is often difficult to detect slight enlargement and to interpret findings which suggest slight enlargement. Because of vagaries of the aortic second sound, this sign, also, has its limitations. Blood pressure is valuable, but it is a well recognized fact that there may be advanced arteriosclerosis without increase of pressure. In addition, there are the uncertainties of blood pressure standards.

FUNDI

The importance of examination of the fundus has been recognized for some time. Changes in the ocular vessels may often be the only evidence of vascular disease.

ROENTGEN-RAY EXAMINATION

Clinical and postmortem data show that disease of the heart and vessels of the lower extremities account for the majority of deaths among diabetics. We have, therefore, included in this study roentgen-ray examination of the heart and lower extremities.

A. Roentgen-Ray Examination of the Heart

The "six foot plate," interpreted by the Hodges and Eyster formula⁶ appears to be a reliable method for classifying hearts for statistical purposes with respect to the size of the organ. The Hodges and Eyster formula was chosen in 1931 by the Heart Committee of the New York Tuberculosis and Health Association as probably the best for this purpose, and a cardiological committee appointed by the Association of Life Insurance Medical Directors of America came to the same conclusion in 1933, after having rechecked the validity of the formula on a sizeable group of normal subjects, the data being taken partly from the literature and partly from the original records of one of the very large companies, which carefully tabulates anthropometric measurements of its head office clerical employees. The committees mentioned were of opinion that a heart should be regarded as definitely enlarged if the

total observed transverse diameter is 10 per cent or more in excess of the predicted normal by the formula mentioned. The observations covered the ages from 15 to 63 years, weights from 100 pounds to 216 pounds, and heights from five feet to six feet, three and one-half inches. Analysis showed that only 8.5 per cent of the group had a total transverse diameter of more than 10 per cent below the calculated normal diameter, and that only 4.2 per cent had transverse diameters of more than 10 per cent in excess of the predicted normal. Three and one-tenth per cent lay between plus 10 per cent and plus 12 per cent, and 1.1 per cent were between plus 12 per cent and plus 20 per cent in excess of the calculated normal. Because of these studies, it was concluded* that ± 10 per cent is a fair upper limit of normality. The permissible limits of departure from the normal in the following studies were, therefore, also ± 10 per cent.

B. Roentgen-Ray Examination of the Extremities

Labbé and Lenfantin⁸ first emphasized the importance of this method of examination and it is now widely used. Experience has shown, however, that this method also has its limitations. Roentgenological diagnosis depends upon deposition of calcium in the vessels and it is a well recognized fact that there may be advanced arteriosclerosis without such deposition.

As each of the above-mentioned methods has its limitations, an attempt was made to determine which method alone or which combination of methods affords the best means of detecting vascular disease.

METHODS OF INVESTIGATION

For this study, 1500 diabetics were selected at random from our records. In many of these cases, examinations did not include all of the above-mentioned methods. In order to make use of all data, each method was studied individually and then in different combinations with each other, whenever the necessary information was available. Brief mention of some of the clinical data is necessary here.

In 146 of the 1500 cases the only suggestive abnormalities were (a) a blood pressure of 140 mm. of Hg or over and (b) the left border of the heart was situated 10.5 cm. or more to the left of the midsternal line. Even in otherwise healthy individuals, when the blood pressure was 140 mm. of Hg, life assurance companies have repeatedly noted an increase of death rate.† However, if such blood pressure is the *only* suggestive abnormality, the applicant is not generally classified as substandard because, in the majority of cases, the finding is normal. This, also, applies to the finding of the left border of the heart at 10.5 cm. to the left of the midsternal line. In the classification of the above mentioned 146 cases, we, therefore, took

* Proceedings Association Life Insurance Medical Directors of America, 1933, xx, 184, Turner, Nichols and Ungerleider.

† I am indebted to Dr. C. C. Birchard, Chief Medical Officer of the Sun Life Assurance Company of Canada, for this information.

In a recent study of over one-half million insured lives, the New York Life Insurance Company has shown that the normal blood pressure is lower than is generally realized. For all ages to age 70, it is below 140 mm. Hg. A systolic pressure of 10 mm. Hg above the average for the age gave an excess mortality of 15 per cent; and a systolic pressure of 25 mm. Hg above the average for the age gave an excess mortality of 45 per cent.

it, when either blood pressure or size of the heart was the only suggestive abnormality, that there was no cardio-vascular disease. When both suggestive abnormalities were found in the same individual, the latter was classified as "cardio-vascular."

A brief note is also necessary here with regard to the fundi. As stated, this method of examination was dealt with separately. It was not included in the ordinary clinical procedures for the following reasons:

Though there is general agreement about the changes in the vessels in advanced vascular disease, there appear to be differences of opinion about early changes. As, in the initial stages, these are no more than exaggerations of the normal appearance, different interpretation by different individuals is only to be expected. This applies particularly to such early changes as congestion; increased diameter of veins; alteration of light reflex, and tortuosity of arteries. For uniformity of data, therefore, all examinations in this study were made by the same individual (S. H. McK.). The criteria were as follows:

Vascular Changes in the Fundus. Alterations in the vessels of the fundi affect both veins and arteries. The first sign observed is a general congestion of the veins which results in an increase of their diameter and a broadening of their light reflex. Next these veins, being made longer by congestion, show bending in the direction of the artery and this bending may be considered a first step in the development of venous tortuosity. Slightly later the phenomenon of disappearance of the vein at the point of intersection with an artery is observed. The vein is invisible, not only directly under the artery, but also for a short distance to either side. This is not necessarily a pressure effect; later a condition is seen in which pressure is definitely evidenced by slight dilatation of the veins just before the artery is reached. A further change in the veins consists of what is called bridging or banking, where the veins are seen to arch over or under the artery, in a more direct transverse axis, a letter Z formation. The final variety of venous change is tortuosity due to increased resistance to venous drainage.

Arterial changes, which usually are observed later, consist of calibre variation, tortuosity, alterations in the light reflex and pressure effects. The changes in calibre may be uneven and patchy in distribution or there may be a uniform narrowing, giving pale threadlike vessels. In some instances the vascular changes may result in regular interruptions of the light reflex without altering the column of blood, a condition which causes a beaded appearance of the artery. The degree of tortuosity of the arteries is very variable; the tendency to small cork-screw arteries in the macular area is important. The changes in light reflex give rise to the appearances known as copper-wire arteries, silver wire arteries, etc.

Retinal hemorrhages and exudates may both result from vascular changes. Evans⁹ believes that a certain type of retinal exudate is definitely associated with arteriosclerosis. It is of a dull yellow color variously distributed; one common situation is the margin of the disc.

The optic disc in retinal arteriosclerosis is usually not much affected until the late states. In advanced degrees of retinal arteriosclerosis there is evidence of a characteristic waxy pallor of the disc due to ischemia.

RESULTS OF INVESTIGATION

In table 2 are recorded the incidences of cardio-vascular disease according to the method of examination. It will be observed that the highest incidence was found with the ordinary clinical method. The limited significance, however, which can be attached to any one procedure alone is clearly shown in tables 3, 4, 5 and 6. In these tables, vascular disease is related to age. It will be observed that, according to roentgen-ray examination of the size of the heart (table 3) very few individuals under the age of 50 years had vascular disease; among 436 patients it was found in 46—an incidence of 10.5 per cent only; it was practically absent at the age of 30 years and under, and entirely absent at the age of 20 years and under.

TABLE II

Incidences of Cardio-Vascular Disease among 1500 Diabetics According to Method of Diagnosis

Method of Examination	Number of Examinations	Cardio-Vascular Disease	
		Number	Per Cent
Clinical*	926	378	40.8
Fundi	984	365	37.1
X-Ray of feet	858	262	30.5
X-Ray of heart	1004	182	18.1

* Cases in which blood pressure and heart measurement data were not recorded in detail were not included in this investigation.

According to calcification of the vessels of the lower extremities (table 4) the findings were practically the same; of 400 individuals of age 50 years and under, vascular disease was detected in 57 cases only—an incidence of 14.2 per cent only, and among 66 individuals of 30 years of age and under, it was detected in two cases only—an incidence of 3 per cent.

TABLE III

Age Incidence of Vascular Disease According to X-Ray Examination of Size of Heart in 1004 Diabetics

Age Period	Total Number	Vascular Disease	
		Number	Per Cent
-10	9	—	—
11-20	26	—	—
21-30	74	2	2.7
31-40	130	8	6.1
41-50	197	36	18.2
51-60	281	57	20.2
61-70	229	61	26.6
71-80	57	18	31.5
81+	1	—	—
	1004	182	18.1
Summary:			
30 years and under	109	2	1.8
50 " " "	436	46	10.5
Over 50 years	568	136	23.9

That roentgenological examination alone was not sufficient to determine the incidence of vascular disease in the group of individuals investigated is shown in the remaining tables. According to the fundi (table 5) among 537 individuals of 50 years and under, there were 111 cases, an incidence

TABLE IV

Age Incidence of Vascular Disease According to Calcification of Vessels in the Lower Extremities in 858 Diabetics

Age Period	Total Number	Calcification	
		Number	Per Cent
-10	5	—	—
11-20	16	—	—
21-30	45	2	4.4
31-40	150	11	7.3
41-50	184	44	23.9
51-60	221	97	43.8
61-70	196	89	46.2
71-80	40	18	45.0
81+	1	1	—
	858	262	30.5
Summary:			
30 years and under	66	2	3.0
50 " " "	400	57	14.2
Over 50 years	458	205	44.7

of 20.6 per cent, and among 69 individuals 30 years of age and under, there were 9 cases, an incidence of 13 per cent. According to ordinary clinical examination, the results were essentially the same. This is shown in table 6.

Do the above findings reflect the conditions which obtain among diabetics? That they do not, is shown in table 7. In this table are recorded

TABLE V

Age Incidence of Vascular Disease According to Examination of Ocular Vessels (Fundi) in 984 Diabetics

Age Period	Total Number	Vascular Disease	
		Number	Per Cent
-10	6	—	—
11-20	19	3	15.8
21-30	44	6	13.6
31-40	192	16	8.3
41-50	276	86	31.1
51-60	252	128	50.7
61-70	146	87	59.6
71-80	48	38	79.1
81+	1	—	—
	984	365	37.1
Summary:			
30 years and under	69	9	13.0
50 " " "	537	111	20.6
Over 50 years	447	254	55.8

the incidences of cardio-vascular disease according to *combinations* of two methods. With four methods taken two at a time, six such combinations are possible. By comparing tables 2 and 7, it will be observed that with

TABLE VI

Age Incidence of Vascular Disease According to Clinical Examination (Excluding Fundi) among 926 Diabetics

Age Period	Total Number	Vascular Disease	
		Number	Per Cent
-10	5	—	—
11-20	28	4	14.3
21-30	66	6	9.1
31-40	136	7	5.1
41-50	176	47	21.0
51-60	258	133	51.5
61-70	213	145	68.0
71-80	44	36	82.2
81+			
	926	378	40.8
Summary:			
30 years and under	99	10	10.1
50 " " "	411	64	15.6
Over 50 years	515	314	60.9

any combination of two methods, the incidence of vascular disease was higher than with any one method alone (table 2). By combining three methods at a time, the incidence was further increased (table 8) and when all four methods were combined the incidence was highest. Among 500 individuals so examined vascular disease was found in 313 cases, an incidence of 62.6 per cent. That this incidence approaches the true conditions which obtain among these diabetics is suggested from tables 9 and 10; the incidences noted clinically approach those which have been found by careful postmortem examination. According to table 9, approximately 55 per cent of our diabetics of 50 years of age and under had vascular disease. Table 10 is a reproduction of table 26 of Shields Warren's "Pathology of Diabetes Mellitus." ⁵ According to Warren, of 108 individuals of age 50 years and under, arteriosclerosis was found in 71 cases, an

TABLE VII

Incidences of Cardio-Vascular Disease among 1500 Diabetics According to Combination of Two Methods of Diagnosis

Method of Examination	Number of Examinations	Cardio-Vascular Disease	
		Number	Per Cent
Fundi and x-ray of feet	739	334	45.2
Fundi and clinical	662	332	50.1
Fundi and x-ray of heart	886	399	45.0
Clinical and x-ray of feet	737	391	53.0
Clinical and x-ray of heart	682	282	41.3
X-Ray of feet and x-ray of heart	760	348	45.8

incidence of approximately 66 per cent. It should be noted, as Warren points out, that the great majority of the individuals in this age group did not die of arteriosclerosis; this condition was the cause of death in seven cases only.

TABLE VIII

Incidences of Cardio-Vascular Disease among 1500 Diabetics According to Combination of Three Methods of Diagnosis

Method of Examination	Number of Examinations	Cardio-Vascular Disease	
		Number	Per Cent
Fundi, clinical and x-ray of feet	620	346	55.8
Fundi, clinical and x-ray of heart	564	341	60.5
Fundi, x-ray of feet and x-ray of heart	642	367	57.2
Clinical, x-ray of feet and x-ray of heart	640	357	55.8

TABLE IX

Incidences of Cardio-Vascular Disease among 500 Diabetics According to Age

Age Period	Number	Cardio-Vascular Disease	
		Number	Per Cent
-10	4		
11-20	14	4	28.6
21-30	34	5	14.7
31-40	67	33	49.2
41-50	124	91	73.3*
51-60	158	106	67.1
61-70	80	59	73.7
71-80	18	14	77.8
81+	1	1	—
	500	313	62.6

* Note: Among 243 individuals of 50 years of age and under, cardio-vascular disease was found in 133—an incidence of 54.7 per cent.

TABLE X

Postmortem Incidences of Arteriosclerosis *

Age at Death (Yrs.)	Number of Cases	Incidence of Arterio-sclerosis	Age at Death (Yrs.)	Number of Cases	Incidence of Arterio-sclerosis
-10	9	0	51-60	66	65
11-20	23	7	61-70	65	65
21-30	19	10	71-80	19	19
31-40	21	19	81+	2	2
41-50	36	35†	?	4	3
			Total	264	225 (85.2%)

* Taken from Table 26, "Pathology of Diabetes Mellitus," Shields Warren.

† Among 108 individuals of 50 years of age and under, arteriosclerosis was found in 71—an incidence of 65.7 per cent.

INFLUENCE OF THE DURATION OF THE DIABETES

In view of the satisfactory diagnosis when all four methods of examination are combined, it was considered advisable to reexamine the alleged relationship between duration of diabetes and cardio-vascular disease. For this purpose, the 500 cases shown in table 9 were studied. Cardio-vascular disease was related not only to age, but also to duration of diabetes. The combined data are shown in table 11.

TABLE XI

Relationship between Cardio-Vascular Disease, Age and Duration of Diabetes among 500 Diabetics

Age Period	Duration of Diabetes					
	5 Years and Over			Under 5 Years		
	Total Number	Cardio-Vascular Disease		Total Number	Cardio-Vascular Disease	
		Number	Per Cent		Number	Per Cent
-10				4		
11-20	2	2	100.0	12	2	16.7
21-30	4	2	50.0	30	3	10.0
31-40	21	18	85.7	46	15	32.6
41-50	54	47	87.0	70	44	62.8
51-60	50	43	86.0	108	63	58.3
61-70	12	8	66.7	68	51	75.0
71-80	1	1	100.0	17	14	82.3
81+				1	1	100.0

It will be observed that in the majority of these 500 cases, namely, 356 (71.2 per cent) there was a history of diabetes of less than five years and, among these 356 cases, cardio-vascular disease was found in 193, an incidence of approximately 55 per cent. In accord with past experiences, a high incidence of vascular disease is expected when the disease is of more than five years' duration; but this high incidence was not suspected when the duration of the disease was less than five years. This emphasizes the value of the *combined* method of examination. It will also be observed in this table that of 162 individuals of 50 years of age and under who had diabetes for five years or less, vascular disease was found in 64 cases—an incidence of approximately 39 per cent.

That this high incidence of vascular disease among individuals of 50 years of age and under and with the disease of less than five years' duration would be discovered by the combined method of diagnosis only is suggested from the following:

In table 7 of a report in 1930 Joslin¹⁰ records the incidence of calcification of arteries according to the ages of the individuals and durations of diabetes in 298 cases. The incidences are expressed as percentages. The 298 individuals are divided into 40 groups. In the majority of cases, therefore, the number in each group was small—less than 10 cases. Since limited significance can be attached to findings with such small groups, and

in order that Joslin's findings may be comparable with our own, we have converted Joslin's percentages into actual number of cases and divided the 298 individuals into three groups only according to age and two groups only according to duration of diabetes. The combined data are summarized in table 12.

TABLE XII
Comparative Data Showing Relationship between Cardio-Vascular Disease, Age and Duration of Diabetes

Age Group	Under 5 Years Duration			Over 5 Years Duration		
	No.	Cardio-Vascular Disease		No.	Cardio-Vascular Disease	
		Number	Per Cent		Number	Per Cent
Whole*	103	52	50.5	195	131	67.2
50 years and under	52	8	15.4	145	83	57.2
Over 50 years	51	44	86.3	50	48	96.0

* Calculated from x-ray data, Table 7, ANN. INT. MED., 1930, iv, 54, E. P. JOSLIN (298 cases).

Age Group	Under 5 Years Duration			Over 5 Years Duration		
	No.	Cardio-Vascular Disease		No.	Cardio-Vascular Disease	
		Number	Per Cent		Number	Per Cent
Whole†	356	193	54.2	144	121	84.0
50 years and under	162	64	39.5	81	69	85.2
Over 50 years	194	129	66.5	63	52	82.5

† The Montreal General Hospital data (500 cases). All methods of diagnosis used.

It will be observed that, regardless of duration of diabetes, the incidence of vascular disease was much higher according to the combined method of examination than when diagnosis was based upon roentgenological examination alone. In Joslin's group of cases, 15.4 per cent only of the individuals of 50 years of age and under had vascular disease, when the duration of the diabetes was less than five years; whereas, in our group, the incidence for the corresponding group was 39.5 per cent. When the duration of the diabetes was more than five years, again, our incidence was higher than that recorded by Joslin for the younger age groups, namely, 85.2 per cent compared with 57.2 per cent.

That our data reflect the true conditions which obtain among diabetics in general is again supported by postmortem data. The observations of Warren,⁵ who has made a special study of the pathology of diabetes, are worthy of note here. "I have yet to see at autopsy a diabetic, or to read the autopsy protocol of a diabetic, whose disease has lasted five years or more, free from arteriosclerosis, regardless of age."

SUMMARY

The purpose of this report is to emphasize the high incidence of vascular disease in diabetes mellitus.

The cause of this high incidence is, as yet, unknown.

Aside from etiology, for the prevention and successful treatment of vascular disease, early diagnosis is essential. The above data indicate that by a combination of the methods investigated vascular disease is more readily detected than by the use of any one method to the exclusion of all others; the incidence of vascular disease found during life approaches that found on careful postmortem examination.

REFERENCES

1. ELLIOTT, A. R.: A clinical study of blood pressure variations in diabetes and their bearing on the cardiac complications, *Jr. Am. Med. Assoc.*, 1907, xlix, 27-30.
2. JANEWAY, T. C.: Important contributions to clinical medicine during the past 30 years from the study of human blood pressure, *Bull. Johns Hopkins Hosp.*, 1915, xxvi, 341-350.
3. SHEPARDSON, H. C.: Arteriosclerosis in young diabetic patient, *Arch. Int. Med.*, 1930, xlv, 674-689.
4. WILDER, R. M.: Necropsy findings in diabetes, *South. Med. Jr.*, 1926, xix, 241-248.
5. WARREN, S.: The pathology of diabetes mellitus, 1930, Lea and Febiger, Philadelphia.
6. HODGES, F. J., and EYSTER, J. A. E.: Estimation of transverse cardiac diameter in man, *Arch. Int. Med.*, 1926, xxxvii, 707-714.
7. TURNER, H. B., NICHOLS, C. F., and UNGERLEIDER, H. E.: A recommended standard for the determination of cardiac enlargement, *Trans. Assoc. Life Ins. Med. Director*, 1933, xx, 184.
8. LABBÉ, M., and LENFANTIN, H.: Les lésions artérielles des diabétiques décelées par la radiographie, *Bull. et mém. Soc. méd. d. hôp. de Par.*, 1924, xlviii, 522-524.
9. EVANS, P. J.: Some aspects of vascular changes in fundus oculi and of retinal arteriosclerosis in particular, *Brit. Jr. Ophth.*, 1933, xvii, 257-286.
10. JOSLIN, E. P.: Arteriosclerosis in diabetes, *ANN. INT. MED.*, 1930, iv, 54-66.

TULAREMIC PNEUMONIA *

By P. G. BOMAN, M.D., and A. J. BIANCO, M.D., *Duluth, Minnesota*

UNTIL recently many observers have considered the presence of pneumonia in cases of tularemia as an intercurrent infection. Several published necropsy reports refer to more or less extensive bronchopneumonia without directly attributing it to the tularemic infection.

Permar and MacLachlan,¹ in reviewing the reported fatal cases, found that 36 per cent showed pneumonia either clinically or at autopsy and that in 62.5 per cent of the autopsied cases there was diffuse pneumonic involvement. In correlating the pathological reports in published cases with their own observations they believe that tularemic pneumonia presents morphologic changes which are specific for tularemia. These morphologic changes are the typical miliary necrotic focal lesion, extreme subendothelial edema and mononuclear cellular infiltration in the blood vessels. The edema in the arterioles and venules produces a narrowing in the lumina of the vessels, which is followed by thrombosis. It is this thrombosis with the resulting vascular obstruction which accounts for the widespread necrosis present in these cases. This necrosis, which is usually progressive, indicates a grave prognosis.²

It is certain that many cases with minimal pulmonary involvement recover³ and that some pneumonias do not go on to a fatal outcome, as evidenced by the case reported recently by Tureen⁴ in which complete recovery occurred.

We have recently observed a case which closely parallels that reported by Tureen and in which complete recovery likewise occurred:

CASE REPORT

A mechanic, aged 37 years, was admitted to St. Mary's Hospital on September 22, 1932 under the care of Dr. Anthony J. Bianco, who had been called to see the patient at his home that same day.

The complaints on admission were chills, fever, headache, general malaise, extreme exhaustion, left sided chest pains, dyspnea and cough. He had been taken suddenly ill four days previously with chills, fever, headache and generalized aches and pains. The day following, a slight unproductive cough had developed and this became progressively worse during the next two days, during which time chest pain and dyspnea also appeared.

At the time of admission to the hospital the cough was severe and prostration was marked. His temperature was 104.8° by rectum, pulse rate 116 and respiratory rate 30. Chest examination showed moderate dullness over the base of the left lung posteriorly and moist inspiratory râles were heard over this same area. A roentgenogram of the chest showed a small area of infiltration in the lower left lobe. The white blood count was 6000. A diagnosis of lobar pneumonia was made and treatment instituted on this basis.

* Read before the Minnesota Society of Internal Medicine, May 15, 1933.
From The Duluth Clinic and St. Mary's Hospital.

On the next day he was definitely worse: prostration had increased, diaphoresis was marked, the cough was severe and he was raising blood stained sputum. The chest pain and headache continued. The temperature rose to 105.4° (R.). The

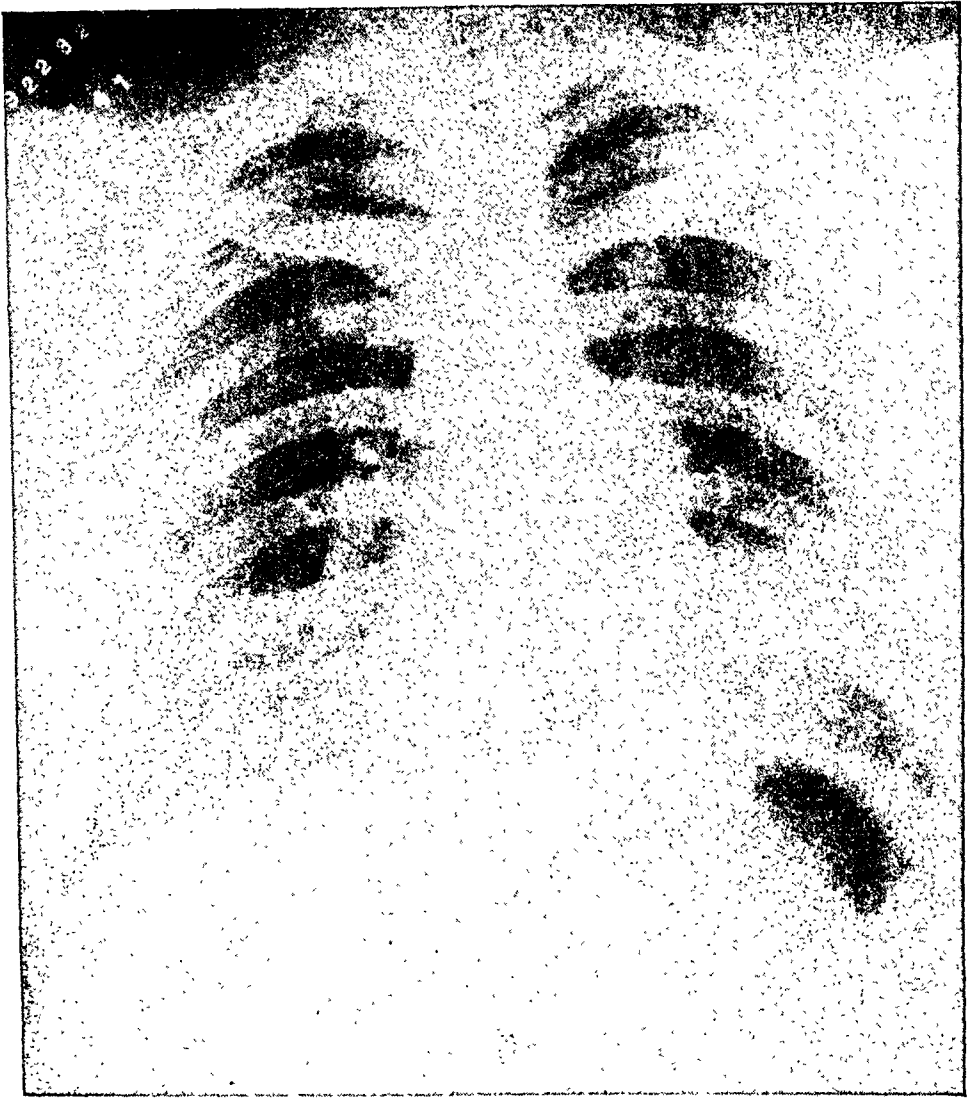


FIG. 1. Roentgenogram of chest on the fourth day of illness, showing moderate involvement of the lower lobe of left lung.

dullness over the left base was increased and bronchial breathing was noted in addition to the inspiratory râles.

On the ninth day of his illness his condition appeared about the same except that cyanosis was present. He was still coughing severely and raising the blood stained sputum. Respirations were more rapid and shallow. Chest examination indicated the presence of a pleural effusion on the left side. The white blood count was 5000, polymorphonuclears 69 per cent, lymphocytes 30 per cent, monocytes 1 per cent. On the next day 600 c.c. of fluid were removed from the left pleural cavity. This showed a white blood count of 1777 and a red blood count of 8200. No microorganisms were found on direct smear and a culture was later reported as negative.

His condition progressively became worse. He appeared to be very toxic, cyanosis increased to a marked degree, and delirium developed. Continuous use of oxygen gave considerable relief and a second thoracentesis was performed.

At this time blood was sent to the Minnesota State Laboratory for agglutination tests because the prostration and toxicity appeared to be out of proportion to the pulmonary involvement. On October 4, 1932 the report from the Minnesota State Laboratory stated that there was complete agglutination of the blood serum with *B. tularensis* in 1:80 dilutions and partial agglutination in 1:160 dilutions. Agglutination was absent with *Brucella melitensis* and *B. typhosus* and *paratyphosus*.

On receiving this report a careful search for a primary lesion and lymph gland

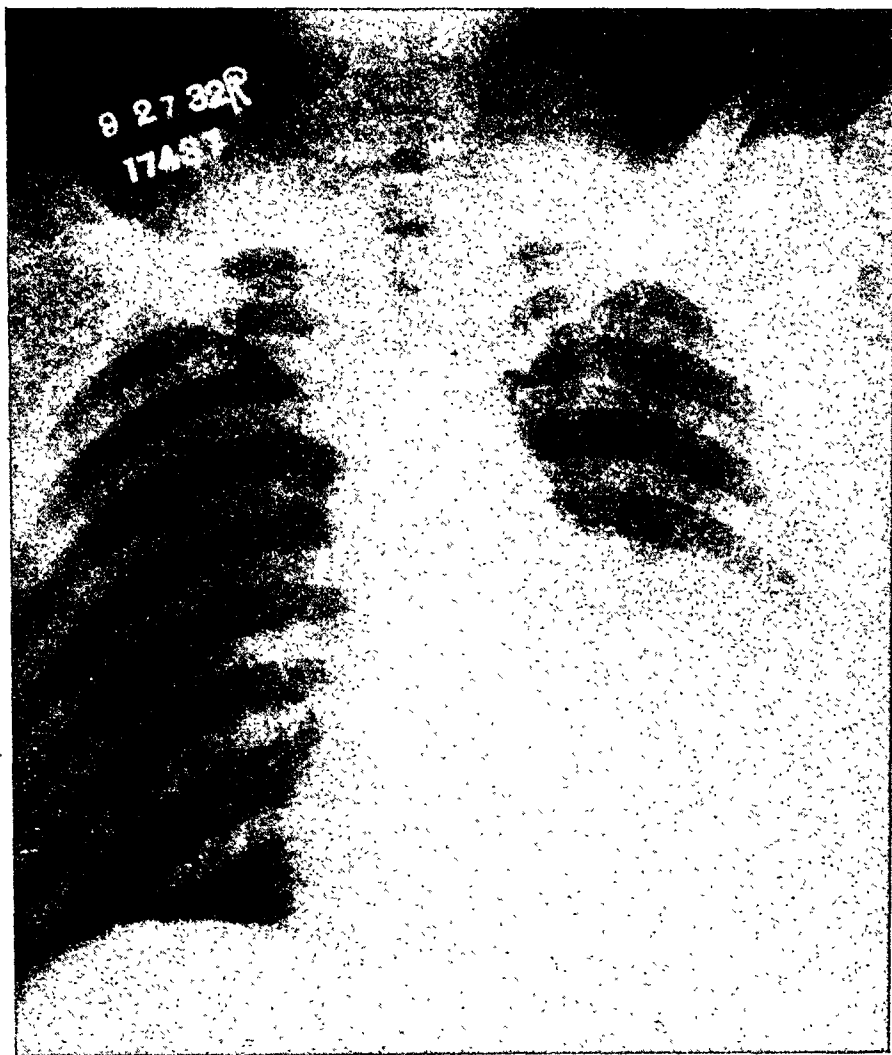


FIG. 2. Roentgenogram taken on the ninth day of illness, showing extension of pathologic process in lower left lobe.

involvement was made but none was found. The patient was irrational and could not give any history of exposure, but his wife stated that he had skinned a rabbit four days before the onset of his illness. (The patient later stated that just before skinning the rabbit he had squeezed a pimple on the median side of the right anterior nares and that while he was skinning the rabbit he wiped the secretion from his nose with his hand. He apparently infected himself through the open sore in his nostril. The nose was sore for several days following this, but he thought that he had a small boil.)

A second blood specimen was sent to the Minnesota State Laboratory on October 7, 1932 and this showed that agglutination was present with *B. tularensis* antigen in dilutions of 1:1280. A definite diagnosis of tularemia and tularemic pneumonia with pleural involvement was now made.

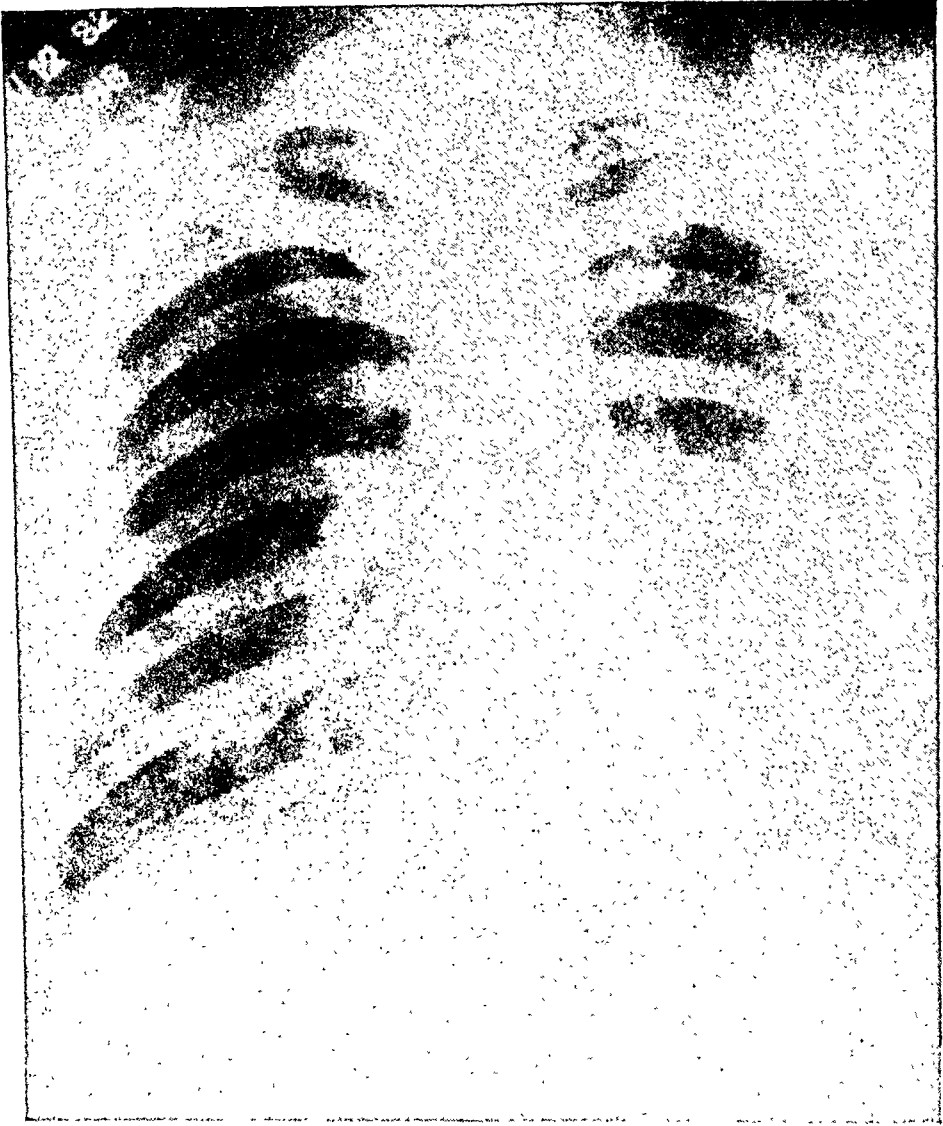


FIG. 3. Appearance of lungs at the end of the seventh week of illness.

On the seventeenth day of his illness the temperature, which had ranged from 102° to 105.4° (R.), began to drop and a gradual improvement was noted. On the thirty-fifth day his temperature was normal and he was transferred to his home to continue his convalescence. At this time he noticed several small pustules on the skin of his body and these persisted for three weeks. A direct smear showed gram-positive diplococci, which were lancet-shaped.

His convalescence was slow, and six weeks after his return home he was able to walk only a short distance without experiencing fatigue and dyspnea. He was able to return to work during the middle of March of 1933—six months after the onset of his illness. He is now in excellent health and shows no evidence of his illness, except that on May 12, 1933 the blood serum showed agglutination with the *B. tularensis*

antigen in dilutions of 1:1280. Agglutination was absent when tested with *Br. melitensis*, *B. typhosus* and *paratyphosus*.

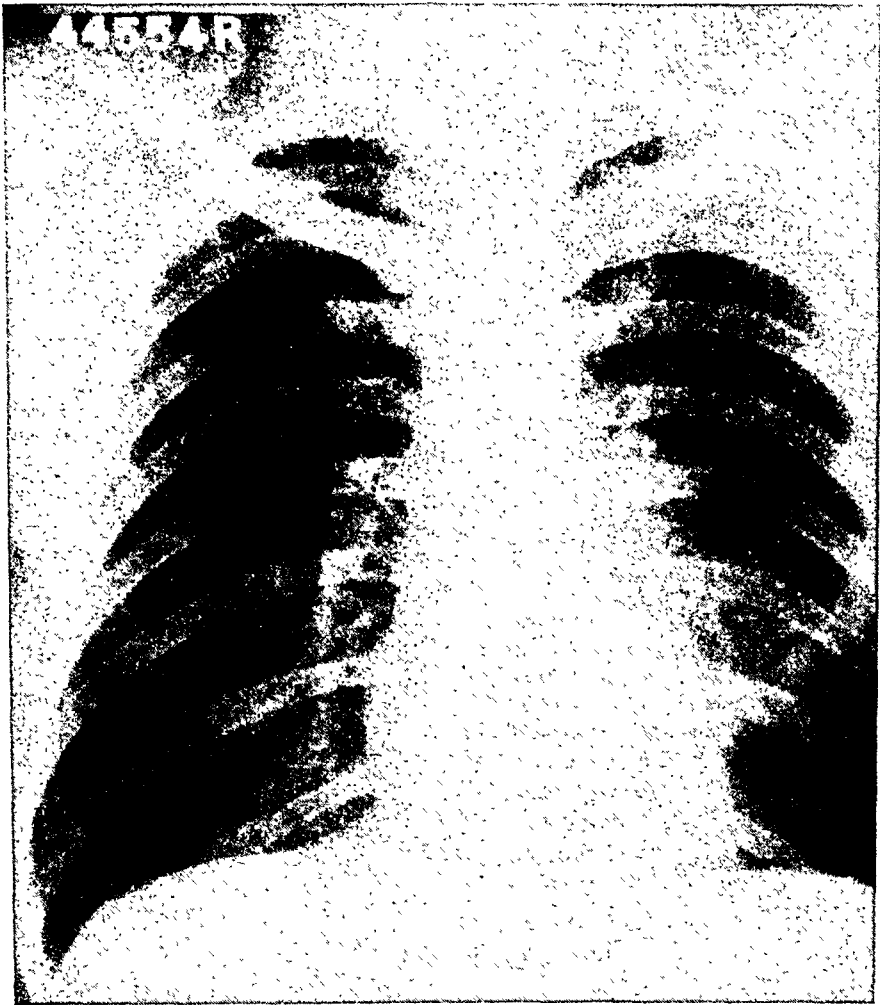


FIG. 4. Normal roentgenogram obtained eight months after onset of illness.

This case is of interest because it presents an instance of severe tularemic pneumonia which resulted in complete recovery after a prolonged convalescence; and also because of the unusual mode of infection.

BIBLIOGRAPHY

1. PERMAR, H. H., and MACLACHLAN, W. W. G.: Tularemic pneumonia, ANN. INT. MED., 1931, v, 687-698.
2. FRANCIS, E.: Symptoms, diagnosis and pathology of tularemia, Jr. Am. Med. Assoc., 1928, xci, 1155-1161.
3. SANTE, L. R.: Pulmonary infection in tularemia, Am. Jr. Roentgenol., 1931, xxv, 241-242.
4. TUREEN, L. L.: Tularemic pneumonia, Jr. Am. Med. Assoc., 1932, xcix, 1501-1502.

DEVELOPMENTS AND DISAPPOINTMENTS IN BLOOD STUDIES *

By ROGER I. LEE, M.D., F.A.C.P., *Boston, Massachusetts*

SOMEWHAT over a medical generation ago, or at the beginning of the present century, the study of blood entered on what seemed to be a remarkably promising era. Hitherto, careful and exact studies of organs and tissues had been carried out largely after death. However, the advances in surgery were encouraging the development of a living pathology in contrast to a postmortem pathology. The internist was eager to study at the bedside the beginnings of disease, rather than to confine his attention to the study of end results in the autopsy room. The possibilities of living studies were obvious and far-reaching in diagnosis, prognosis and treatment, and perhaps the most alluring tissue for such study was the blood, which touched every part of the body, and on which indeed life itself depended.

Up to this time the clinician had the thermometer as his usual instrument of precision, his stethoscope as an assisting mechanical device, and the examination of the urine as his important clinical laboratory test. There had already been developed to a considerable extent the numerical and the morphological study of the formed elements of the blood. The anemias and the leukemias were recognized as blood diseases in which the diagnosis could be best made by the examination of the blood. In his picture of the possible development of studies of the blood, the clinician looked forward to the collection of data concerning the living patient, which would in connection with his clinical ability and the already developed pathological postmortem experience furnish accurate and complete diagnosis and prognosis and rational and precise treatment, with possible and even probable cure of most diseases.

The development of a technic in immunology—of which the common illustration was the agglutination reaction for the typhoid bacilli—gave high hopes for the value of blood studies in immunology. The so-called Widal reaction stood up nobly under the acid test of experience and there seemed to be no reason why similar methods might not prove applicable to many, if not all, of the infectious diseases in which the causative organism could be isolated and grown on artificial media. At the same time that the agglutination and other antibody reactions were being studied, the technic of cultures was being developed, and it was confidently predicted that by the examination of the blood by blood cultures and by the reactions of the serum and of the formed elements of the blood, the precise diagnosis of nearly all, if not all, infectious diseases would be attained.

A little later perhaps, but essentially simultaneously, studies in blood chemistry were being pushed and it seemed reasonable to expect that the

* Read before the American College of Physicians, Chicago, April 16, 1934.

analysis of a specimen of blood could detect not only such recognized diseases as nephritis, diabetes, gout, and the like, but also the exact chemical status of the body. It seemed probable at that time that studies of the blood would solve many of the mysteries in regard to metabolism. There was much speculation as to a possible precise correlation between the chemical analysis of the blood and diet. Possibly if some important constituent were lacking, that deficiency might be supplied directly to the blood, if simpler methods were ineffective.

As one looks in retrospect upon these very active and indeed very fruitful years, one finds that the optimistic hopes of a generation ago are far from being fulfilled. As we survey the advances in what might be called morphological studies, we find that we have a larger and considerably clearer conception of the so-called formed elements of the blood. But this is amplification of knowledge that in the main already existed rather than important discoveries. This is even true of the blood platelets which are now recognized as separate entities, and it is generally accepted, I think, how the blood platelets are formed and the usefulness of the blood platelets in the promotion of coagulation and in clot retraction. Studies along these lines have given us a far better concept of many of the recognized blood diseases and have established the identity of certain conditions associated with a low number of blood platelets such as thrombopenic purpura. That the blood platelets are normal morphologically but function in an abnormal fashion in hemophilia, is slowly gaining credence. Dr. W. H. Howell, at the Baltimore meeting of the American College of Physicians, stated his present leaning toward that theory after many years of study of hemophilia.

Hematological studies have brought into our ken such disorders as sickle-celled anemia and granulopenia. The hemolytic anemias have been clarified. The definite establishment of blood groups, even if all the refinements of the problem are by no means elucidated as yet, has given to the clinician the necessary safeguards in employing transfusion as a therapeutic procedure. Certainly blood transfusion stands out clearly as a definite product of blood studies during this period. Furthermore, in order to establish the rôle of blood transfusion as a safe therapeutic procedure, not only were studies of compatibility in regard to red corpuscles and sera necessary, but also studies in regard to blood coagulation, blood volume and other aspects were almost equally important. In addition, all these studies of the various factors which make for safe blood transfusion have vastly helped our understanding of the blood as a whole, as well as the fundamental interrelation of red blood corpuscles and the blood plasma or blood serum. As an illustration of a development out of the study of these factors, mention may be made of the determination of the sedimentation rate of the red corpuscles. The variations of this rate depend upon alterations in the normal interrelation of red corpuscles and plasma.

I would be far from decrying any of the advances in microscopic hematology, and yet it must be admitted that, as a reward of a prodigious amount

of work, there has been with one great and glorious exception mostly a better understanding of certain clinical conditions already recognized rather than great discoveries. Of course, the great and glorious exception to which I refer is the demonstration of the successful control of pernicious anemia by the administration of liver or some kindred substance. It is important, I think, to appreciate the fact that this great discovery obviously and properly takes, by the very nature of the therapeutics, the disease long known as a primary blood disease quite out of that category and makes it a purely secondary blood disease. It is of interest in this connection, however, that the work which culminated in this startling demonstration was done by investigators who were concerning themselves almost exclusively with blood studies and who were trying to determine the effect of diet upon blood.

The studies of the white corpuscles of the blood, morphologically and otherwise, have been disappointing. Within limits we have increased our knowledge of the leukemias. But, as an example, we are still at as much loss concerning acute leukemia as we ever were. Has it any relation to the other leukemias anyway?

The leukocytic response to the various infections is perhaps held in lower esteem than it was 25 years ago. We accept without great excitement the general fact that certain infections usually but not always have a characteristic leukocytic response. Indeed one such infection is frequently called infectious mononucleosis. There are recurrent waves of interest in the fact that the responding polynuclear leukocytes may have the characteristics of youth or that under certain stimulations bizarre cells may be present in the blood stream. Of course these findings have some significance, but the significance is mild. The special study of the leukocytes by such methods as the opsonic index of Wright certainly has not given that wealth of information so confidently predicted early in this century.

In the field of bacteriology and immunology, the blood has been subjected to extremely intensive study. Our ability to grow microorganisms out of the blood has been, at least up to now, limited to only a few of the many infectious diseases and has been frankly disappointing. Of course when successful it is a procedure of great value. It may well be that our technic is at fault and that we await the advent of another Pasteur who will again combine intellectual genius and imagination with the technic of a true virtuoso in his field. Or it may be that the field of blood cultures has produced its harvest and there will be no important additional crops in the way of tangible results.

There have been many studies tending to demonstrate the activity of the blood and the organism in general in combatting the infectious diseases. It has been mostly the blood serum which has been subjected to this study and various important reactions have been determined. In some instances, the findings are not important from a diagnostic or an immediately applicable therapeutic view but are very important in the general concept of the

particular disease. Curiously enough, the best known of these serological tests is an adaptation of the complement fixation phenomenon. This was at one time considered to be a specific biological test for syphilis. It is indeed a most curious and most extraordinary fact that this test which became most famous as the Wassermann test is not in any sense a specific biological reaction at all. Even today, we do not know why the blood serum of syphilitic patients gives this type of reaction under the conditions of this test in such a remarkably accurate percentage. It is an interesting commentary that a whole generation should have passed and should have accepted the outstanding and obvious fact that the Wassermann test is such a valuable adjunct to medical practice and nevertheless should still have to grant that the underlying basis is quite unknown. However, the complement fixation phenomenon is used with satisfactory results in a modest number of infectious diseases. In these circumstances the test is essentially specific.

Disappointing as a good many of these studies have been in the production of specific and tangible clinical tests directed toward the infections and the body response to them, and however much we may point out the fact that the best known test is not a specific biological test but a pure accident, the underlying mechanism of which is unknown, nevertheless, in this field of immunology really very great advances have been made in our understanding of the complicated mechanism of the infectious diseases. The studies of the family of the streptococcus depend considerably upon a multitude of serological reactions in the human patient and in the experimental animal. Even if the retrospect shows much that is disappointing, and certainly the retrospect falls short of fulfilling even what was called a generation ago modest expectations, nevertheless, substantial progress has been made. And the end is not yet. Perhaps the future has in store some antibody reaction, possibly of a nature now unsuspected, which will give to the clinician his long awaited precision test in the infections.

The chemist, always interested in the blood, found great difficulty in getting an adequate amount of blood *in vivo* for chemical study until it was determined that blood could easily be obtained from the veins. Thereafter, the chemist busied himself with devising methods for the estimation and study of all sorts of chemical substances in the blood, with particular reference to those substances concerned in metabolism and its disturbances and in some of the common diseases. As I have indicated before, at one time it was thought that a careful chemical study of the blood would give us an exact picture of any individual, his metabolism and its disturbances, and might indeed represent an estimate of the efficiency of his total bodily functions. It was early found that the estimation of blood sugar was of very great importance in the diagnosis and control of diabetes and of any interference with sugar metabolism. Additional experience through the years has confirmed this test as highly satisfactory in clinical practice. The various tests for the determination of the different nitrogenous substances

in the blood have not proved quite so satisfactory. While it is true that in many cases of advanced renal disturbance one gets a high retention of certain nitrogenous substances in the blood, yet the determination of these substances is really of little importance in the early stages and, as might be expected also, a variety of conditions other than kidney damage often bring about an abnormally high reading of these nitrogenous substances in the blood. The single illustration of the effect of starvation upon the blood chemistry and particularly the nitrogenous substances will be sufficient to give my meaning. The determinations of the calcium and the phosphates in the blood have developed into important findings in certain rather restricted clinical conditions and the same is true of various other substances such as chlorides, etc. It was hoped at one time that the chemical examination of the blood might enable us to understand the mechanism of edema, particularly those forms of edema which are certainly in their general essence not mechanical. Curiously enough, there has been a bitter disappointment in studies along these lines and even after the exhibition of successful therapeutic agents the study of the blood during the actually enormous polyuria and the disappearance of edema has frequently shown no significant change chemically.

Certain rather more complicated studies of the blood, particularly those directed toward the study of the acid-base equilibrium of the blood and the variations therein, and the chemical studies of certain so-called buffer salts have been very helpful to our understanding of the fundamental physical and chemical changes which go on in the body and have had unquestionably a considerable influence upon our general knowledge of clinical conditions and indeed upon the general clinical attitude in therapeutics. Nevertheless, the extravagant hopes of extensive precise application of these studies to definite clinical problems have not been realized.

When, however, the blood studies have been directed toward the particular function of the blood of delivering oxygen to the tissues and removing carbon dioxide therefrom, and when these blood studies are combined with correlated studies of respiration and of the circulation, we find that very notable progress has been made in the fundamental physiology and secondarily in many clinical pictures. Upon this better understanding, definite therapeutic measures are clinically based. These studies have indicated that any interference with what might be called the hemodynamics, or in other words the circulation of the blood, is obviously just as serious as any interference with the content of the blood. These studies, furthermore, have indicated that the blood content, even in the very restricted sense of the amount of oxygen and carbon dioxide, is dependent upon such factors as altitude, atmospheric pressure, etc. Furthermore, any substantial deviation from the usual total volume of the blood is accompanied by marked interference of the capacity of the blood to perform its function in the gas exchange of oxygen and carbon dioxide.

Certainly, as one contemplates in retrospect these blood studies, morphological, serological, bacteriological, immunological, chemical, and physical, one must sense the fact that the outstanding function of the blood seems to be to act as the vehicle for the gas exchange of oxygen and carbon dioxide between the tissues and the outside atmosphere. In that sense the blood acts as a vehicle, and if there is interference with the load that it carries or with the vehicle itself, there is inevitably some disturbance. If one carries this thought further, one finds indeed that one can build up a satisfactory conception of the blood as a vehicle. For example, before the present era, the diagnosis of Bright's disease, or nephritis as we now call it, was made by very careful examination of the urine. With the advance in the technic of chemical blood studies, we have gotten one stage nearer the source of disturbance, but the blood chemistry does not reveal necessarily the whole picture. The disease is in certain organs and tissues. The actual disturbance is very largely in certain fixed cells. The blood merely acts as a vehicle which may or may not show the intensity of this disturbance. The intensity of this disturbance is reflected in the blood when the cells give off certain abnormal products if these products remain in the blood and can be chemically demonstrated. It is possible to assume that the cells might not give off abnormal products, although they were badly damaged, and indeed it is likely that the rate of output of these abnormal products does not precisely correspond with the degree of damage. Here again, the blood represents a vehicle or means of communication between the cell and the elimination from the body. Likewise, in bacteriological and immunological studies, bacteria may be present in the blood stream for possible destruction or elimination. This mechanism occurs in some diseases and does not occur in others. In some instances of infection, the antibodies seem to circulate freely in the blood; in others they seem to be fixed in the cells. There is as wide a variation in that aspect as there is in the appearance of a leukocytosis in one kind of infection, the appearance of a lymphocytosis in another, and of no demonstrable change in the formed elements of the blood in others. In other words, the blood may or may not show any alteration or any of the evidences of existing tissue disturbance. This may be true even though there be tissue reactions in the bone marrow, the lymph gland, or the more obscure tissue reaction of those cells which deal with the complicated production of some of the antibodies.

It would seem to me that if we accept the blood as a vehicle and indeed as hardly an organ of itself, it would tend to clarify our fundamental ideas in regard to blood as a tissue. We must grant the fact that even in diseases of the blood as pernicious anemia, now controlled even if not cured by diet, or in leukemia, which frequently can be controlled for some time by irradiation, and in which we may get a normal blood picture in the course of some infection, the blood may show at times essentially no deviation from normal. All this indicates that the blood is hardly a primary tissue in a somewhat

arbitrary sense. It is true that the blood is one step nearer the cell than the urine and often gives us unquestionably more information. Nevertheless, sometimes it may be technically simpler to discover clinically certain substances in the urine than it is in the blood—for example, the hormone of pregnancy. However, in the final analysis, the cells of the body are the real subjects of our study and it seems to me that we must assume that the blood is one step removed from the cells and that in all of our blood studies, we are not studying, with the exception of gas exchange and a few other things, the fundamental cell itself or its disturbance. Consequently, I believe that we should interpret all blood studies in this light and regard them mostly as indicators rather than actual positive fundamental facts of bodily disturbance. In that light, it seems to me that while we may have had many and bitter disappointments in our blood studies of the past generation, and while we must admit that we were far too optimistic in our hopes and predictions, and while we were at fault in hoping to find something which the studies themselves have shown could not have been present, nevertheless these blood studies have brought about a profound and fundamental clarification of many of the complicated mechanisms of the body and I hope have brought about a clearer concept of the blood itself and of the function of the blood.

Perhaps some virtuoso of technic, or better many virtuosos, may in the future develop some different angles in blood studies. It may be that some time the scrutiny of the blood will furnish precise indicators of cellular activity and of cellular disturbance. But our present knowledge leads us to assume that with the exception of the hemodynamic function of the blood, blood studies will be important as determining indications of functions and diseases rather than the actual functions and processes themselves.

MULTI-PLANE CHEST ELECTROCARDIOGRAPHY

A STANDARDIZED METHOD OF CHEST LEAD APPLICATIONS *

By JOSEPH WEINSTEIN, M.D., *Brooklyn, New York*

SINCE the introduction of the string galvanometer by Einthoven¹ in 1903, and the perfection of the modern electrocardiograph, a multitude of experiments were conducted to determine the most suitable points for the application of the electrodes, with the final acceptance of the three limb "leads" now universally adopted. The electrocardiograms thus produced have proved of invaluable assistance to the clinician in the study of cardiac irregularities and affections of the myocardium.

That this method has its limitations has been shown by the frequent occurrence of proved cases of coronary vessel occlusions where normal electrocardiograms were obtained. The reason is that the three standard leads represent a single plane and will, therefore, fail to record changes in the muscle action current in "silent areas" of the heart muscle which travel in a different axis.

Lewis² in 1909 first observed the advantage of an antero-posterior chest lead in his observations on the auricular action in fibrillation. In 1932 Wolferth and Wood^{3,4} definitely established the advantage of an antero-posterior chest lead (which they called "Lead IV") in cases of coronary occlusion. Similar findings were observed by Lieberman and Liberson,⁵ Katz and Kissin,⁶ and others.

Wood and Wolferth⁷ observed, in cases of experimentally produced coronary occlusions in dogs, that the electrocardiogram produced by a single antero-posterior lead may fail to show the presence of the myocardial change when other chest leads, where the electrodes are applied to the surface of the body in the proper locations, will definitely demonstrate the lesion. They also noted that the maximum changes were observed in the leads applied nearest the lesion. Hoffman and Delong⁸ demonstrated clinically the advantage of using several antero-posterior chest leads placed at arbitrarily selected points, having observed that the lesion may be detected on one or two of these leads and not on any of the others.

These observations indicate the necessity of a wider range of accurately standardized application of chest lead take-offs. The method which I propose will, I believe, not only detect more readily changes in all "silent areas" of the myocardium, but will also give a better index as to the location of the lesion. With the use of long electrodes, applied as in figures 1 and 2, the heart is surrounded and intersected by "planes" of action current take-off.

* Received for publication February 26, 1934.
From the Medical Service of the Jewish Hospital of Brooklyn.

TECHNIC

The right and left arm electrodes are used for the chest application and they are so placed that the current take-off is kept in the same relationship to the current direction within the heart as in the three standard limb leads. Figure 3 illustrates (as presented by Pardee⁹) the relation of the current direction within the heart to that obtained by the right and left arm electrodes as applied in Lead I. The right arm electrode is, therefore, always

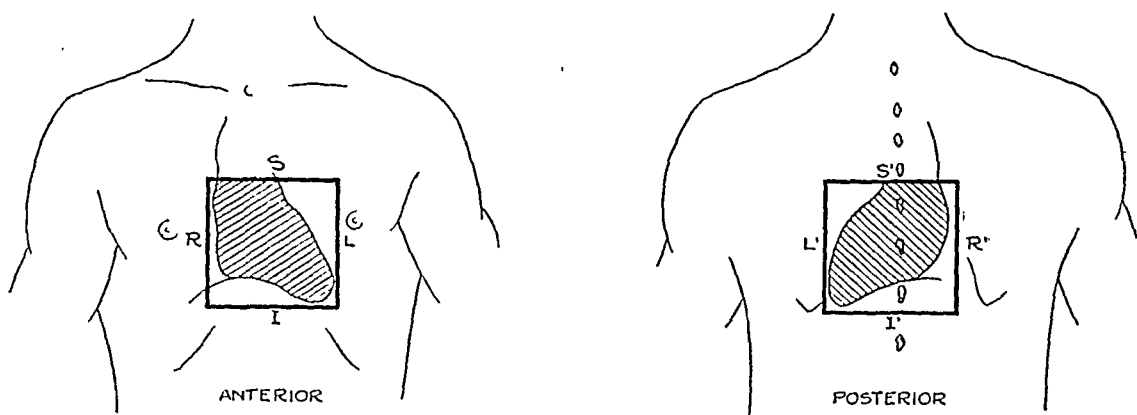


FIG. 1. Illustration of the positions for the application of the electrodes. Their length and location are dependent on the size of the heart.

On the anterior chest wall: *R* is a vertical line at the right border of the heart extending from about the level of the right chondrosternal junction downward. *L* is a vertical line at the left border of the heart at the same level as *R*. *S* is a horizontal line at the superior border of the heart extending from the upper end of *R* to the upper end of *L*. *I* is a horizontal line at the inferior border of the heart extending from the lower end of *R* to the lower end of *L*.

On the posterior chest wall: Positions *R'*, *L'*, *S'* and *I'* are determined by the extension of positions *R*, *L*, *S* and *I* directly posteriorly to the posterior chest wall.

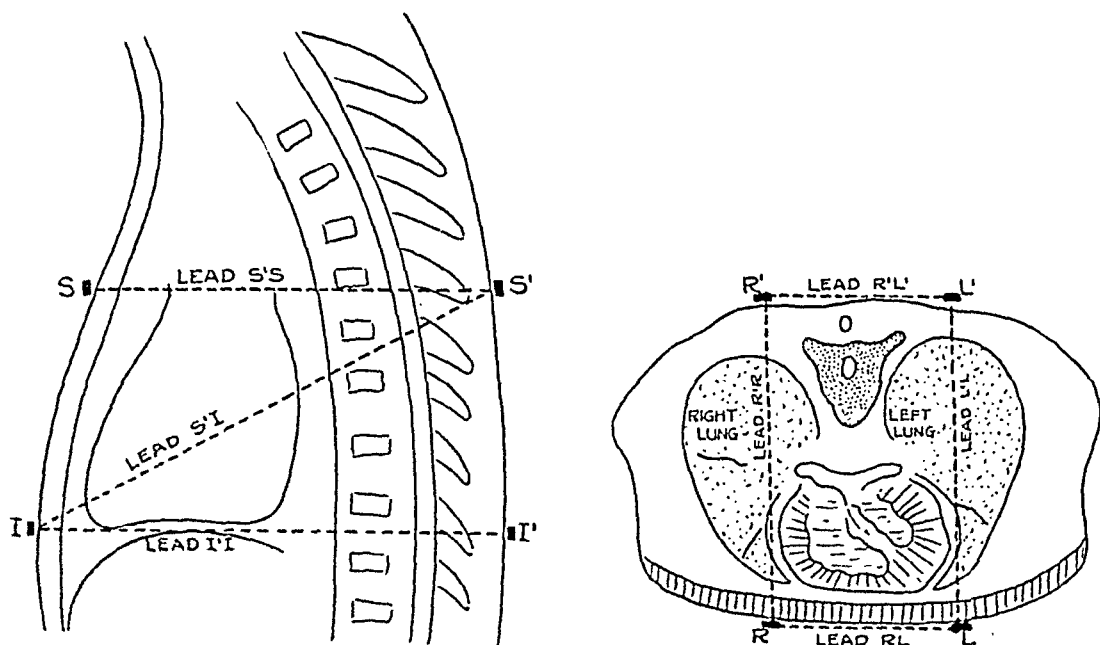


FIG. 2. Lateral and cross section views of the chest illustrating the positions for the application of the electrodes.

applied to the chest in closest relation to the tail of the arrow, while the left arm electrode is applied in closest relation to the head of the arrow representing the heart action current direction.

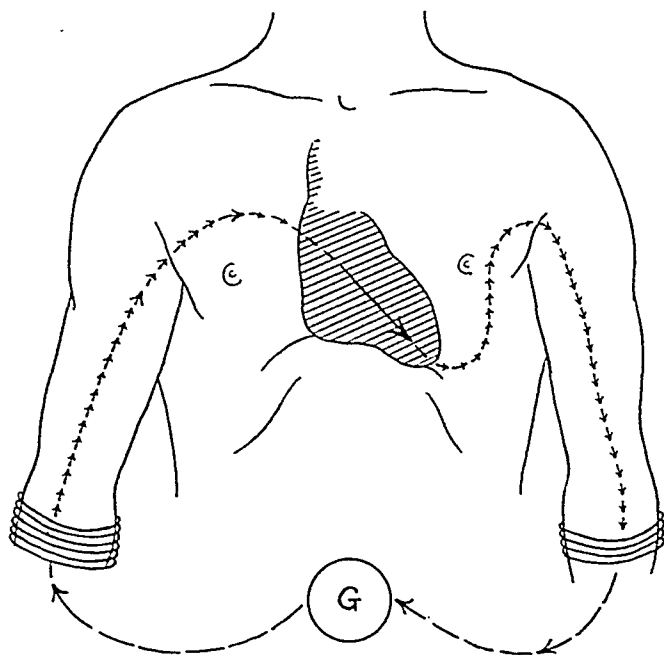


FIG. 3. (As illustrated by Pardee.⁹) Diagram showing the relation of the current within the heart to that obtained by Lead I. The line of arrow heads passing through the body from right arm to left arm represents the flow of current in Lead I, and the circuit is completed outside the body through the galvanometer as indicated by the long dotted arrows between the two arms.

It is important accurately to determine the size of the heart and the position of the cardiac borders either by a teleroentgenogram, fluoroscopic methods, or by as accurate percussion as is possible.

Flexible electrodes, $\frac{1}{2}$ inch wide and from four to six or more inches in length, depending on the size of the heart, are used. The electrodes should be covered with gauze soaked in warm saline solution. The skin at the sites selected is cleansed with an antiseptic solution, and linear scarifications, the length of the electrodes used, are made. The electrodes are held firmly in place either by an assistant whose hands are insulated with rubber gloves or, preferably, by a spring clamp device. The skin resistance should be carefully standardized before each lead is taken.

The electrodes are applied to the positions on the chest wall as illustrated in figures 1 and 2.

Leads	Right Arm Electrode Applied to Position	Left Arm Electrode Applied to Position
R'R	R'	R
L'L	L'	L
RL	R	L
R'L'	R'	L'
S'S	S'	S
I'I	I'	I
S'I	S'	I

RESULTS

Normal Controls

A study of 50 normal cases gave strikingly uniform tracings on all the multi-plane chest leads. Figure 4 illustrates three normal cases taken from this group. Both the standard limb leads and the multi-plane chest leads are shown. The time element remains the same as on the standard limb leads. An analysis of the normal multi-plane chest leads reveals the following:

Lead R'R—A low upright or biphasic P-wave, a prominent S- and a low upright T-wave.

Lead L'L—A low or iso-electric P-wave, a biphasic QRS, and an upright symmetrical T-wave.

Lead RL—A low upright P-wave, a prominent R- and a low S-, upright symmetrical T-wave.

Lead R'L'—A low upright P-wave, a prominent R- and a low symmetrical T-wave.

Lead S'S—A low upright or biphasic P-wave, a prominent S- and a low upright T-wave.

Lead I'I—An upright P-wave, biphasic QRS of high amplitude, and a very high symmetrical T-wave measuring from 5 to 10 mm. in height.

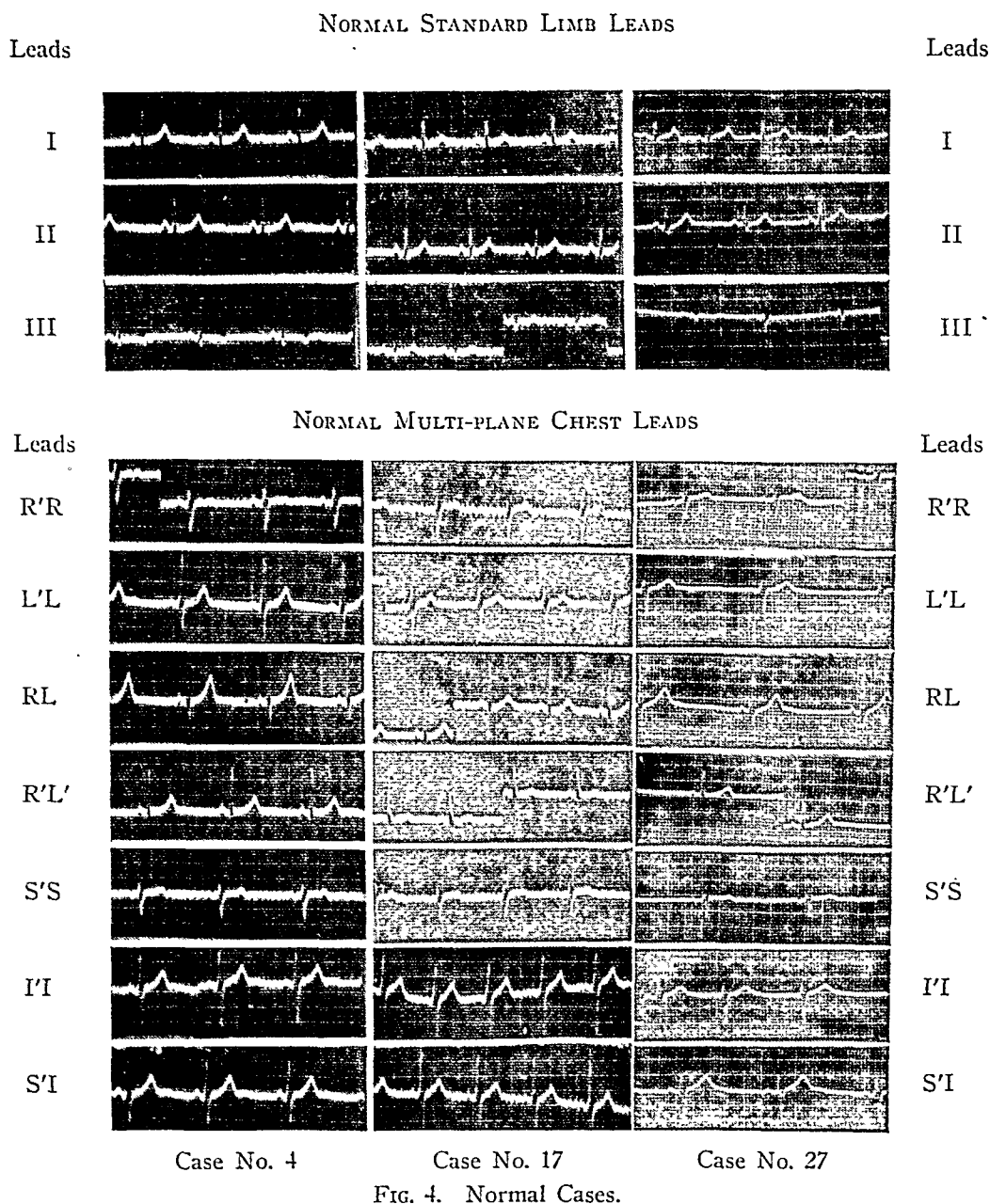
Lead S'I—A prominent upright P-wave, a biphasic QRS of high amplitude, a very high symmetrical T-wave measuring from 5 to 10 mm. in height. A prominent U-wave is frequently observed on this lead.

Cases Presenting Abnormal Multi-Plane Chest Leads

The following patients, although showing comparatively normal tracings in the three standard limb leads, presented definite abnormalities in the multi-plane chest lead tracings.

Case 5 (figure 5), a young male, 30 years of age, gave absolutely no symptoms referable to his cardio-vascular system. The physical examination was entirely negative. The standard limb lead tracings showed no abnormalities other than a slight (0.5 mm.) elevation of the RT transition of Lead II. However, the multi-plane chest leads showed a definite inversion of the P- and T-waves on Leads R'R and S'S, a 1.5 mm. elevation of the RT transition above the iso-electric line on Lead L'L and a saddling and 2.5 mm. elevation of the RT transition above the iso-electric line on Leads I'I and S'I. A careful review of the past history of the patient revealed the fact that a few months previously he had had an influenzal bronchopneumonia which was followed by a toxic exhaustive state which lasted about three weeks.

Case 26 (figure 5), a male, 55 years of age, with a history of hypertension of many years' duration, had been complaining for the past three months of attacks of severe precordial pain, lasting as long as half an hour, coming on with slight exertion and requiring absolute rest for relief. The standard limb leads, in this case, also showed relatively normal tracings with the exception of a left ventricular preponderance; but the multi-plane chest leads showed an inversion of the P- and T-waves in Leads R'R and S'S, a 1 mm. elevation of the RT take-off on Lead L'L and a saddling and a 3 mm. elevation of the RT transition above the iso-electric line on Leads I'I



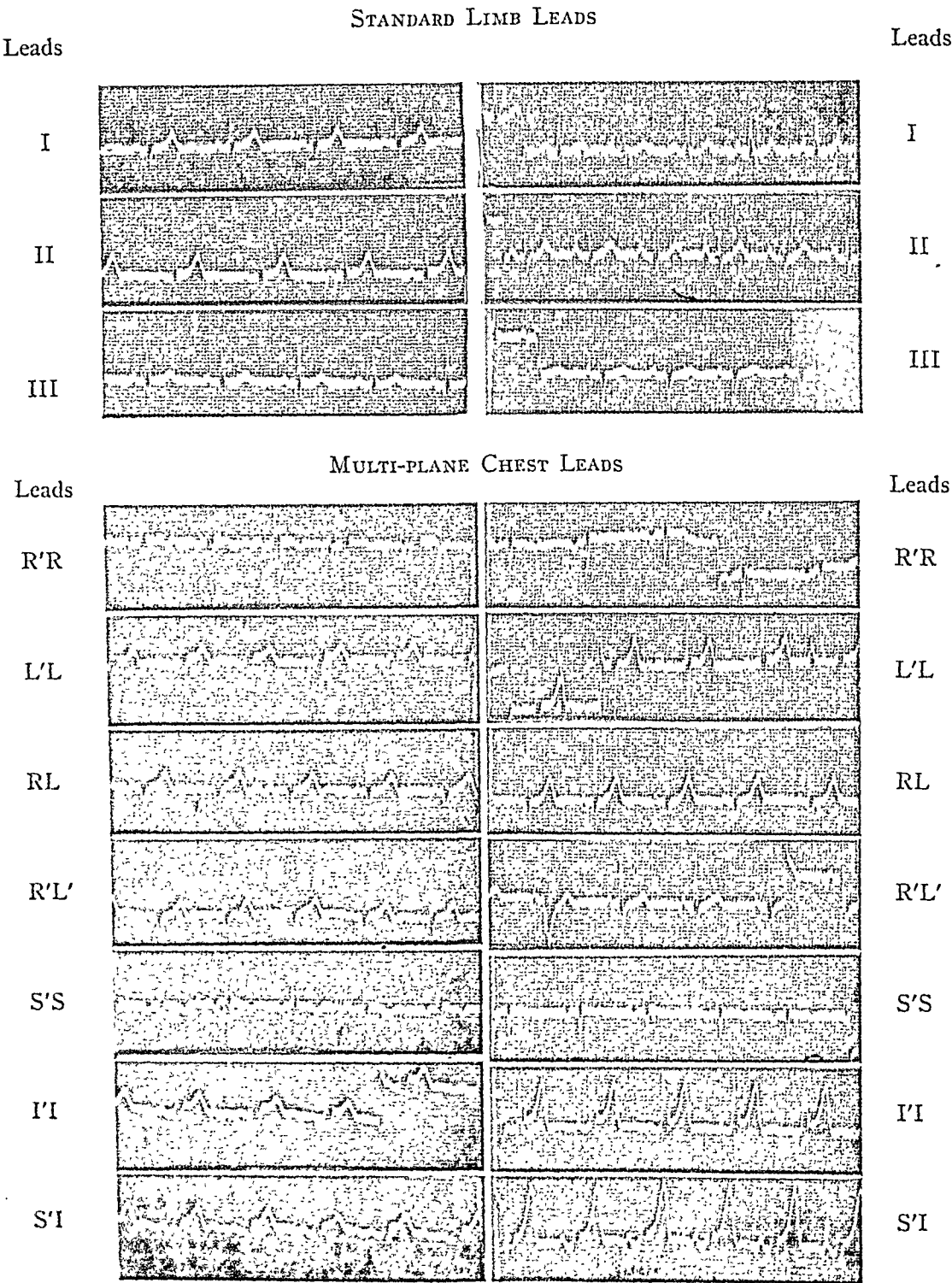
and S'I with very high T-waves. The patient died four weeks after he was examined in an attack of acute coronary thrombosis of 12 hours' duration. Consent for a post-mortem examination was not obtained.

The following two patients showed definite changes in both the standard and the multi-plane chest leads.

Case 11 (figure 6), a male, 55 years of age, gave a history of a chronic, non-specific pulmonary infection of many years' duration. In the past five years he had had repeated attacks of cardiac decompensation. His clinical picture revealed evidence of predominantly right heart failure as evidenced by extensive venous stasis,

a large tender liver, sacral and ankle edema. A roentgen-ray examination of the chest revealed a bilateral hilum and basal infiltration, a widened aorta and enlargement of the heart to both the right and left.

Case 31 (figure 6), a female, 36 years of age, gave a history of an essential hypertension, complaining primarily of headaches and dizziness for many years. For



Case No. 5 Case No. 26

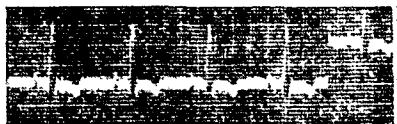
FIG. 5.

the past year she had suffered with palpitation, dyspnea and precordial pain on exertion requiring rest for relief. Clinically there was no evidence of cyanosis, liver enlargement, edema or other evidence of right heart failure. Roentgen-ray examination revealed a widened aorta and an enlargement of the heart to the left. The patient

STANDARD LIMB LEADS

Leads

I



II

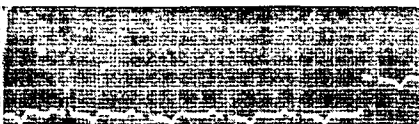


III

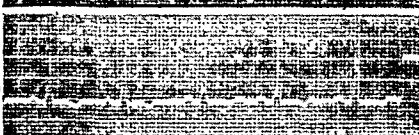


Leads

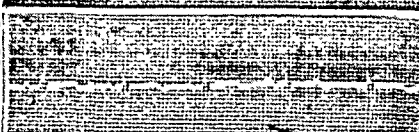
I



II



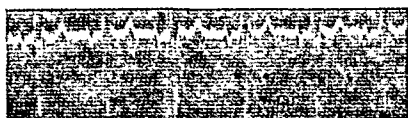
III



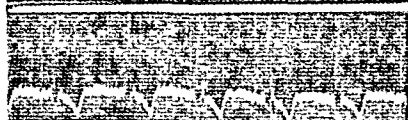
MULTI-PLANE CHEST LEADS

Leads

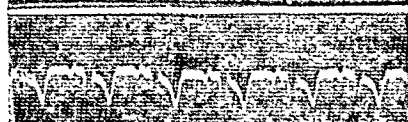
R'R



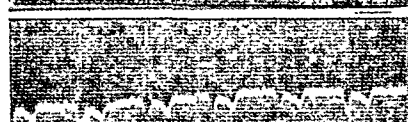
L'L



RL



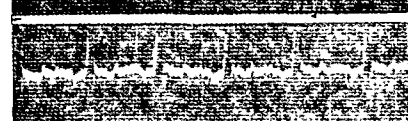
R'L'



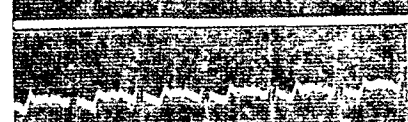
S'S



I'I

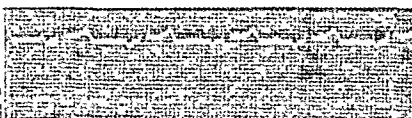


S'I

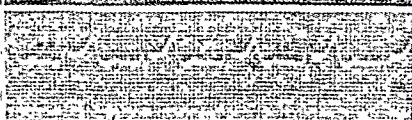


Leads

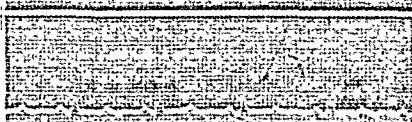
R'R



L'L



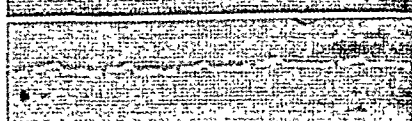
RL



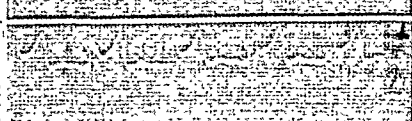
R'L'



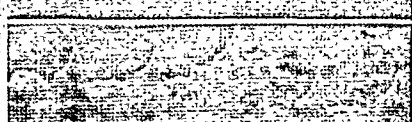
S'S



I'I



S'I



Case No. 11

Case No. 31

FIG. 6.

died in an acute coronary attack six weeks after she was examined. Postmortem examination of the heart revealed a sclerosis and narrowing of the left coronary artery and an occlusion by a fresh thrombus of its anterior descending branch. There was a myomalacia of the anterior wall of the left ventricle extending to the apex. The right coronary tree was found patent throughout.

The standard limb lead tracings show evidence of severe myocardial damage in both cases but without any definite differential localizing features. The following is a comparative study of the changes in the multi-plane chest lead tracings of the two cases.

<i>Leads</i>	<i>Case 11</i>	<i>Case 31</i>
R'R	Inverted P, prominent S, saddling of RT transition, upright T-wave.	Inverted P, prominent S, elevation of RT transition 1 mm. above iso-electric line, upright T-wave.
L'L	Iso-electric P, prominent R, sharply inverted deep T-wave.	Low upright P, biphasic slurred QRS, elevation of RT transition 1.5 mm. above iso-electric line, upright T, prominent U-wave.
RL	Biphasic P, prominent Q, prominent R, slightly depressed RT transition, markedly inverted deep T-wave.	Upright P, prominent R, low upright T-wave.
R'L'	Upright P, prominent R, slightly depressed RT transition, inverted coved T-wave.	Upright P, prominent R, inverted T-wave.
S'S	Inverted P, prominent slurred S, low upright T-wave.	Biphasic P, prominent slurred S, elevation of RT transition 1 mm. above iso-electric line, upright T-wave.
I'I	Inverted P, biphasic QRS of high amplitude, elevation of RT transition 1 mm. above iso-electric line, biphasic T-wave.	Low upright P, prominent S, saddling and elevation of RT transition 3 mm. above iso-electric line, upright high T, prominent U-wave.
S'I	Biphasic P, biphasic QRS of high amplitude, biphasic T-wave.	Upright P, prominent S, elevation of RT transition 2.5 mm. above iso-electric line, upright high T, prominent U-wave.

COMMENT

In the first two abnormal cases presented, although the standard limb lead tracings appeared to be within normal limits, examination of the multi-plane chest lead tracings revealed definite changes from the normal controls (table 1). These consisted of inversion of the P- and T-waves in Leads R'R and S'S, a marked elevation of the RT transition in Leads I'I and S'I and a slight elevation of the RT transition in Lead L'L. In case 5, the influenzal bronchopneumonia and its sequelae are cited as possible etiologic factors in explaining the myocardial changes observed, while case 26 presented clinically the typical syndrome of advanced coronary artery disease.

Of the next two abnormal cases presented, even though the standard limb lead tracings showed definite myocardial damage in both, they presented no definite differential localizing features; while with the multi-plane chest leads, case 11, which clinically gave a picture of predominantly right heart

TABLE I

Leads	Clinical Considerations	Standard Limb Leads	Multi-plane Chest Leads						
			R/R	L/L	RL	R'L'	S/S	I/I	S/I
Case 4 Case 17 Case 27	Normal cases	Normal tracings	Low upright or biphasic P Prominent S Low upright T	Low or iso-electric P Biphasic QRS Upright symmetrical T	Low upright P Prominent R Low S Upright symmetrical T	Low upright P Prominent S Low upright T	Low upright or biphasic P Prominent S Low upright T	Upright P Biphasic QRS of high amplitude Very high symmetrical T	Prominent upright P Biphasic QRS of high amplitude Very high symmetrical T Prominent U often observed
Case 5	No cardio-vascular symptoms. Negative physical examination. (Attack of influenza bronchopneumonia followed by toxic ex-haustive state a few months previously.)	Normal tracings except for a slight (3 mm.) elevation of RT transition of Lead II.	Inverted P Low R Prominent S Inverted T	1½ mm. elevation of RT transition	Normal tracing	Normal tracing	Inverted P Inverted T	Saddling and 2½ mm. elevation of RT transition	Saddling and 2½ mm. elevation of RT transition
Case 26	Hypertensive heart disease Coronary artery disease	Normal tracings except for a left ventricular preponderance and slight slurring of complexes	Inverted P Inverted T	1 mm. elevation of RT transition	Normal tracing	Normal tracing	Inverted P Inverted T	Saddling and 3 mm. elevation of RT transition Very high T	Saddling and 3 mm. elevation of RT transition Very high T
Case 11	Chronic pulmonary infection. Right heart failure (venous stasis, large tender liver, sacral and ankle edema).	Inverted coved T ₁ Depressed RT transition and diaphasic T ₂ Depressed RT transition and upright T ₃	Biphasic P Prominent S Saddling of RT and upright T	Iso-electric P Prominent R Sharply inverted deep T	Biphasic P Prominent Q Prominent R Slightly depressed RT transition Sharply inverted deep T	Upright P Prominent R Slightly depressed RT transition Inverted coved T	Inverted P Prominent slurred S Low upright T	Inverted P Biphasic QRS Elevation of RT 1 mm. Biphasic T	Biphasic P Biphasic QRS Biphasic T
Case 31	Hypertensive heart disease Coronary artery disease	Inverted coved T ₁ and T ₂ Diaphasic P ₃ and T ₃	Inverted P Prominent S 1 mm. elevation of RT transition Upright T	Low upright P Prominent S 1½ mm. elevation of RT transition Upright high T Prominent U	Upright P Prominent R Low upright T	Upright P Prominent R Inverted T	Biphasic P Prominent slurred S 1 mm. elevation of RT transition	Low upright P Prominent S Saddling and 3 mm. elevation of RT transition Upright high T Prominent U	Upright P Prominent S 2½ mm. elevation of RT transition Upright high T Prominent U

involvement, presents an entirely different series of tracings from case 31, whose clinical picture indicated predominantly left heart involvement. The abnormalities here noted have been repeatedly observed and appear to be common in these clinical types of cases.

The interpretation of abnormal tracings obtained by the multi-plane chest lead method and their correlation with the clinical phenomena will be discussed in a later communication. The application of this method in experimentally produced lesions in cats is, at present, being investigated.

SUMMARY

A standardized method of chest lead application which surrounds and intersects the heart by planes of current take-off is proposed.

The uniformity of the tracings obtained in a control group of 50 normal cases is observed.

The advantage of the multi-plane chest leads in conjunction with the three standard limb leads in more accurately detecting and localizing myocardial lesions is suggested.

I wish to express my appreciation to Dr. Meyer A. Rabinowitz, Attending Physician to the Jewish Hospital of Brooklyn, for his coöperation, and to the "B" cardiology service of the hospital for the use of their facilities.

BIBLIOGRAPHY

1. EINTHOVEN, W.: Ein neues Galvanometer, *Annalen der Physik*, 1903, xii, 1059.
2. LEWIS, T.: Auricular fibrillation and its relationship to clinical irregularity of the heart, *Heart*, 1909-1910, i, 306-372.
3. WOLFERTH, C. C., and WOOD, F. C.: Electrocardiographic diagnosis of coronary occlusion by use of chest leads, *Am. Jr. Med. Sci.*, 1932, clxxxiii, 30-35.
4. WOLFERTH, C. C., and WOOD, F. C.: Further observations upon use of chest leads in electrocardiographic study of coronary occlusion, *Med. Clin. North Am.*, 1932, xvi, 161-167.
5. LIEBERSON, A., and LIBERSON, F.: Value of posterior-anterior chest lead in cardiac diagnosis, *ANN. INT. MED.*, 1933, vi, 1315-1321.
6. KATZ, L. N., and KISSIN, M.: Study of Lead IV; its appearance normally, in myocardial disease, and in recent coronary occlusion, *Am. Heart Jr.*, 1933, viii, 595-607.
7. WOOD, F. C., and WOLFERTH, C. C.: Experimental coronary occlusion, *Arch. Int. Med.*, 1933, li, 771-788.
8. HOFFMAN, A. M., and DELONG, E.: Standardization of chest leads and their value in coronary thrombosis and myocardial damage, *Arch. Int. Med.*, 1933, li, 947-964.
9. PARDEE, H. E. B.: Clinical aspects of the electrocardiogram, including the cardiac arrhythmias, 3d Ed., 1933, Paul B. Hoeber, New York, p. 4.

MALARIA THERAPY IN ASYMPTOMATIC NEUROSYPHILIS*

By PAUL A. O'LEARY, M.D., F.A.C.P., *Rochester, Minnesota*

THIS is a report of the results of treatment with malaria of a group of patients who had asymptomatic neurosyphilis. Under the classification of asymptomatic neurosyphilis are included those cases in which tests of spinal fluid are positive, but in which there are neither signs nor symptoms of syphilitic involvement of the central nervous system. The length of time the patient has had syphilis is not a factor in the incidence of asymptomatic neurosyphilis, for its presence may be demonstrated any time after the infection has been acquired. It has been known for some time that the nervous system becomes invaded at the time of dissemination of the *Spirocheta pallida*; in fact, evidence of invasion of the central nervous system can be demonstrated in certain cases before the "secondaries" have become manifest on the skin or mucous membranes. It has been shown that the spinal fluid is abnormal in 32.7 per cent of cases of acute syphilis, including those in which the patient has a chancre but is serologically negative, as well as those in which late secondary manifestations are present. Moreover, reports¹ indicate that the spinal fluid of from 18 to 35 per cent of patients with latent syphilis is positive to test. Asymptomatic neurosyphilis can be recognized only by examination of spinal fluid obtained either by lumbar or by cisternal puncture. Accordingly, in view of the relatively high incidence of this type of neurosyphilis, it is imperative that examination of spinal fluid be made in all cases of acute syphilis some time during the first year of treatment, and in all cases of latent syphilis in which the patients are about 60 years of age or less.

Moore has called attention to the fact that the incidence of serologic cure in cases of asymptomatic neurosyphilis is dependent on the type of neurologic invasion as indicated by the nature of the findings on examination of spinal fluid. For example, if the spinal fluid gives evidence of only a mild degree of involvement, as evidenced by a negative or weakly positive Wassermann reaction, a positive Nonne reaction, slight pleocytosis (between 20 and 50 cells per cubic millimeter), and a negative or syphilitic type of colloidal curve (benzoin or mastic), the serologic response to treatment is usually very rapid and satisfactory in the majority of cases. An example of the severe type of involvement is the case of asymptomatic neurosyphilis in which the spinal fluid gives a strongly positive Wassermann reaction, a strongly positive Nonne reaction, a zone I or parietic type of colloidal test, and the cell count is 50 or more per cubic millimeter of fluid. In such cases the response to treatment is satisfactory in from 30 to 50 per cent of the

*Read before the American College of Physicians, Chicago, Illinois, April 16, 1934.
From the Section on Dermatology and Syphilology, The Mayo Clinic.

cases only. Between these two extremes of cases in which results are good and cases in which results are poor are many cases, in the majority of which the serologic response to treatment will be satisfactory, but in some of which serologic positivity will be retained in spite of the intensive application of arsphenamine, bismuth, and mercury.

Sufficient evidence has now been accumulated to allow the assertion that the patient with asymptomatic neurosyphilis whose spinal fluid does not become negative, and thereafter retain its negativity, either from intensive treatment or his own resistance, is a potential candidate for parenchymatous or vascular neurosyphilis. In such a case tabes dorsalis or paralytic dementia eventually is prone to develop. There is another group of patients known as "chronic relapsers" whose spinal fluid completely reverts to negative following treatment, but who subsequently have neurorelapses with recurrence of positivity of spinal fluid when treatment is stopped. The appearance of clinical signs and symptoms of neurologic involvement is also the rule with these patients.

Accordingly, the program of treatment of asymptomatic neurosyphilis should be materially influenced by the type of invasion of the central nervous system as revealed by reports of tests on the spinal fluid. In those cases in which invasion of the nervous system is of mild degree, routine use of arsphenamine, with either mercury or bismuth, usually produces complete and permanent serologic negativity after four courses of treatment (24 injections of arsphenamine and 60 injections of bismuth as a minimum). If invasion of the central nervous system is of moderate degree, as evidenced by the spinal fluid findings, such a routine course of treatment may not produce serologic reversal, and it then may be necessary to augment the treatment. It has been my practice in this type of case, if the first course of arsphenamine does not bring about material signs of improvement as evidenced by serologic tests of spinal fluid, to intensify the treatment by addition of intraspinal injections, daily intramuscular injections of the succinimide of mercury or of a preparation of bismuth, and liberal use of sodium or potassium iodide. Contrary to the general impression, I have found intraspinal therapy to be of decided value in this type of case. Three or four combined courses may be necessary to maintain negativity of spinal fluid.

In the case of asymptomatic neurosyphilis in which the original spinal fluid factors are strongly positive, and the colloidal test is of the paretic type, the use of the therapeutic measures which I have mentioned may not reverse the serologic tests to negative, or the reversal to negative may be only temporary, and as soon as treatment is discontinued the spinal fluid may again become positive. I have observed cases of asymptomatic neurosyphilis in which a favorable serologic response failed to appear even though more than 100 injections of arsphenamine, with corresponding amounts of mercury, had been given. The explanation of these therapeutic failures may be: (1) therapeutic inefficiency of the remedies, (2) resistance of the in-

fecting organism (resistant neurotropic strain of the *Spirocheta pallida*), or (3) inadequacy of the soil (lack of resistance).

In regard to inefficiency of drugs, it may be said that a sufficiently large number of patients with asymptomatic neurosyphilis have been treated successfully by arsphenamine and heavy metals to emphasize the value of these specific remedies in controlling the majority of the cases. Accumulated statistics show that approximately 85 per cent of patients with asymptomatic neurosyphilis derive satisfactory response from treatment. The failures must be attributed to some other factor than the inefficiency of the drugs. In the laboratory animal a neurotropic strain of *Spirocheta pallida* can be demonstrated to have special affinity for its nervous system. However, in the human being such a demonstration is lacking; in fact, clinical appraisals have failed to substantiate the existence in man of such a strain.⁵ Advocates of the concept that there is a strain neurotropic to man have not as yet proved their contention. The soil on which the *Spirocheta pallida* lights is of more significance in determining the subsequent course of the disease than is the strain of the *Spirocheta pallida*. Therefore, the explanation for many of the failures in treatment of asymptomatic neurosyphilis is attributable to the patient and not to the infecting organism. In other words, the factor of resistance seems to be the most important of the three concepts which are offered in an effort to explain failures of treatment in these cases.

Accordingly, malaria was sought as an agent to stimulate the defensive mechanism of a group of patients in treatment of whom the intensive use of arsphenamine, mercury, and bismuth had failed to produce negative tests of spinal fluid. In 1926 I inoculated with *Plasmodium vivax* a patient with asymptomatic neurosyphilis who had received an enormous amount of anti-syphilitic treatment but whose spinal fluid had remained positive. I selected malaria therapy because two years' experience with it at that time had impressed on me the value of the method in the treatment of dementia paralytica, and it was hoped that it would be of equal value in the prevention of this condition.^{3, 4}

In the past 10 years I have inoculated with malaria 89 patients who had asymptomatic neurosyphilis. Sixty-three of these have reported back recently enough to warrant serologic appraisal. Most of these patients had previously been given the advantage of treatment with arsphenamine, mercury, and bismuth, in varying degrees of intensity, but had failed to obtain satisfactory serologic changes. Clinical signs and symptoms of neurosyphilis were not present in any of the cases. A course involving 12 episodes of chill and fever was given, following which progress of the malaria was stopped by administering quinine sulphate. The patients were then observed for six months or a year without treatment of any type, at the end of which time the spinal fluid was reexamined. If the spinal fluid at that time gave evidence of definite improvement, observation was continued for six months or a year longer. On the other hand, if the report did not give evidence of improvement, the patient was again given arsphenamine,

mercury or bismuth, and intraspinal injections, or, if these were not employed, tryparsamide, and bismuth were administered.

A compilation of serologic changes discloses that in 58 per cent of the cases in which the central nervous system was invaded to a mild degree, and in 30 per cent of those in which it was invaded to a severe degree, the reaction of the spinal fluid was completely reversed to negative as a result of the malaria therapy alone (table 1). In a group of 41 cases in which

TABLE I
Malaria Therapy only (22 Cases). Results as Reflected in Reaction of Spinal Fluid

Results of Original Examination of Spinal Fluid	Cases	Completely Reversed to Negative, Per Cent	Partially Reversed to Negative, Per Cent	Not Improved, Per Cent
Mildly to moderately positive	12	58 (7 cases)	16 (2 cases)	26 (3 cases)
Strongly positive; paretic	10	30 (3 cases)	50 (5 cases)	20 (2 cases)
Totals	22	44	33	23

the customary antisyphilitic treatment was given after malaria therapy, satisfactory serologic reversals were noted in 40 per cent of the cases in which the spinal fluids were mildly involved, and in 31 per cent of the cases in which the spinal fluids were severely involved (table 2). It is obvious

TABLE II
Malaria Therapy Followed by Special Antisyphilitic Treatment (41 Cases). Results as Reflected in Reaction of Spinal Fluid

Results of Original Examination of Spinal Fluid	Cases	Completely Reversed to Negative, Per Cent	Partially Reversed to Negative, Per Cent	Not Improved, Per Cent
Mildly to moderately positive	22	40 (9 cases)	23 (5 cases)	32 (7 cases)
Strongly positive; paretic	19	31 (6 cases)	42 (8 cases)	26 (5 cases)
Totals	41	35.5	32.5	29

that an appraisal of malaria therapy can be based only on the cases in which no other treatment was given. It has been my practice to estimate the serologic results at intervals of six or twelve months after the course of malaria, and if the serologic reports did not give evidence of improvement, the patient was again given the customary antisyphilitic treatment. Accordingly, the patients noted in table 1 included those who received early benefit, and also several who did not return for reexamination until several years had elapsed following malaria treatment, but when they did return

their spinal fluids were reported as negative. The malaria treatment was given in an effort to augment the specific remedies and not to supplant them

TABLE III

The Entire 63 Cases* Which Could Be Followed. Results are Reflected in Reaction of Spinal Fluid

Results of Examination of Spinal Fluid	Cases	Completely Reversed to Negative, Per Cent	Partially Reversed to Negative, Per Cent	Not Improved, Per Cent
Mildly to moderately positive	40	50	28	22
Strongly positive; parietic	23	39	39	22
Total	63	44.5	33.5	22

* Status unknown, 19; died since course of malaria from causes other than syphilis or malaria, 5; died as result of malaria, 1; relapsed, 1.

entirely; hence, the inclusion of all of the cases in table 3 is warranted. In other words, when it was found that malaria alone was not producing serologic reversals, the accepted antisyphilitic agents were used intensively in a further effort to ward off development of parenchymatous neurosyphilis. Table 3 shows that in 44.5 per cent of the group as a whole, the spinal fluid became negative serologically. Another decade must elapse before appraisal of this group of cases for signs and symptoms of neurosyphilis will be of significance. However, it is worthy of comment that up to the present none of the patients included in this study has given clinical evidence of late neurosyphilis. For the present, estimation of the results can be based only on

TABLE IV
Summary of Case 1

Date	Blood, Wasser- mann	Wasser- mann	Nonne	Spinal Fluid		Colloidal Benzoin	Treatment
				Cells per Cubic Milli- meter			
3-28-29	++++	+++ -	+	179* 24† 45‡	333 313 333 320 000		Arsphenamine (1.8 gm.) (6)
							Mercuric succinimide (0.33 gm.) (33)
							Sodium iodide intravenously (19.5 gm.) (30)
							Intraspinal injections (3)
11- 7-29	++++	+++ -	+	37	333 303 233 210 000		Inoculation Malaria
9-28-32	22- -	—	—	3	000 000 333 310 000		No treatment
2- 7-34	1- - -	—	—	1	000 002 333 100 000		No treatment

* Small lymphocytes.

† Large lymphocytes.

‡ Polymorphonuclears.

the serologic changes in patients observed for a period varying from three to ten years following malaria therapy.

A few illustrative cases are cited to emphasize the character of the serologic changes.

CASE REPORTS

Case 1. (Table 4.) The patient was a woman, aged 37 years. A history of syphilis could not be elicited. The diagnosis of asymptomatic neurosyphilis was made in 1929 as a result of a routine Wassermann test of the blood and an examination of spinal fluid.

Case 2. (Table 5.) A man, aged 21 years, had a chancre and a macular eruption in April 1928. Treatment was started immediately, but following the second course he stopped taking treatment, to return in a year with a cutaneous recurrence. He permitted another year to elapse following the fourth course and returned with a neurorecurrence.

TABLE V
Summary of Case 2

Date	Blood, Wasser- mann	Wasser- mann	Nonne	Spinal Fluid		Colloidal Benzoin	Treatment
				Cells per Cubic Milli- meter			
5-16-28	44						Bismarsen (1.6 gm.) (8)
7-17-28	44						Bismarsen (1.6 gm.) (8)
5-22-29	44	—	—	5	Cutaneous recurrence	000 000 333 100 000	Bismarsen (1.6 gm.) (8)
8-13-29	44						Bismarsen (1.6 gm.) (8)
6-23-30	43	42 ---	+	7	Neurorecurrence	000 000 332 000 000	Arsphenamine (6) Mercuric succinimide (24)
10- 9-30	43	4441-	+	14* 23†		000 002 333 000 000	Inoculation Malaria
2-24-33	1-	—	—	1		000 003 333 110 000	No treatment
4- 6-34	1-	—	—	2		000 001 333 300 000	No treatment

* Small lymphocytes.
† Large lymphocytes.

Case 3. (Table 6.) A laborer, 34 years of age, acquired syphilis in 1915, for which he was given 15 mercury rubs. A diagnosis of asymptomatic neurosyphilis was made in May 1922.

Case 4. (Table 7.) A Greek, aged 32 years, acquired syphilis in 1915. Treatment was started immediately, and by 1922 he had received 46 injections of arsphenamine with unknown amounts of mercury (by injection and by mouth). A positive spinal fluid was recognized at this time, so he went to Vienna where he was given intravenous injections of typhoid vaccine and injections of tuberculin. He came under my care in 1925.

Case 5. (Table 8.) A young woman was found to have a positive Wassermann

test of the blood in 1924 and a positive spinal fluid test in 1925. When she came under my care in 1926, she had received 48 injections of arsphenamine and 48 injections of mercuric salicylate.

TABLE VI
Summary of Case 3

Date	Blood, Wasser- mann	Spinal Fluid				Treatment
		Wasser- mann	Nonne	Cells per Cubic Milli- meter	Colloidal Benzoin	
5- 7-22	++++	++++	+	41		Arsphenamine (3.8 gm.) (6)
11- 9-22	++++	++++	+	89	333 333 333 333 000	Mercuric succinimide (27) Arsphenamine (2.5 gm.) (6)
9- 1-23	++ - -	++ -	+	41	023 320 333 322 000	Mercuric succinimide (21) Arsphenamine (3.1 gm.) (10)
1- 8-24	-	++ - -	+	2	000 000 333 200 000	Mercuric salicylate (16.0 gm.) (8) Arsphenamine (3.3 gm.) (10)
6-28-24	-	++ - -	+	1	000 000 232 000 000	Mercuric salicylate (10.0 gm.) (10) Intraspinal in- jections (4) Tryparsamide (18.0 gm.) (6)
2- 8-25	-					Bichloridol (15.0 gm.) (10) Tryparsamide (28.0 gm.) (10)
10-11-25	-					Bismuth (2.0 gm.) (13) Tryparsamide (28.0 gm.) (10)
2-22-26	-					Bismuth (2.0 gm.) (14) Tryparsamide (29.0 gm.) (10)
7- 6-26	-	2 - - -	+	4	002 000 333 200 000	Bismuth (4.0 gm.) (20) Tryparsamide (28.0 gm.) (10)
3- 4-27	-	++ - -	+	18	133 313 331 000 000	Bismuth (4.0 gm.) (20) Inoculation Malaria
8- 1-27	-	-	-	1	011 003 331 000 000	No treatment
2- 1-28	-	-	-	3	000 001 320 000 000	No treatment
2- 2-29	-	-	-	1	000 002 333 100 000	No treatment
9- 1-30	-	-	-	1	000 000 333 100 000	No treatment
8-13-33	-	-	-	1	000 001 333 100 000	No treatment

TABLE VII
Summary of Case 4 after Patient Came under Author's Care

Date	Blood, Wasser- mann	Spinal Fluid			Colloidal Benzoin	Treatment
		Wasser- mann	Nonne	Cells per Cubic Milli- meter		
9-15-25	—	4441-	+	33	011 100 333 100 000	Arsphenamine (2.3 gm.) (6) Mercuric succinimide (0.23 gm.) (20) Sodium iodide (13 gm.) (20) Intraspinal in- jections (3) Mercurial in- jections (40)
3- 5-26	—	444- -	+	27	023 300 333 200 000	Arsphenamine (2.7 gm.) (7) Mercuric succinimide (0.24 gm.) (24) Sodium iodide (13 gm.) (20) Intraspinal in- jections (4) Bismuth (at home) (10)
9- 1-26	—	441- -	+	5	233 300 333 200 000	Arsphenamine (2.3 gm.) (6) Bismuth (1.8 gm.) (18) Bismuth (at home) (15)
2- 9-27	—	421- -	+	14	023 300 333 000 000	Inoculation Malaria
2-11-28	—	—	+	4	011 003 330 000 000	No treatment
8- 6-29	—	—	—	1	000 000 033 200 000	No treatment
7-21-30	—	—	—	1	000 000 333 100 000	No treatment
1- 3-34	—	—	—	1		No treatment

SUMMARY

In the past 10 years 89 patients who had asymptomatic neurosyphilis were treated with malaria when the serologic tests on the spinal fluid had failed to become reversed to negative following intensive use of arsphenamine, mercury, and bismuth. In 50 per cent of the cases in which invasion of the nervous system was of mild degree, the serologic reactions became completely negative following malaria therapy, irrespective of whether anti-syphilitic treatment was given after induction of malaria. In 39 per cent of cases in which the formula of the spinal fluid was of the paretic type, the spinal fluid factors were reversed to negative following malaria therapy. Among those cases in which the usual antisiphilitic treatment was not given following malaria treatment, there was satisfactory reversal to negative of the spinal fluids in 58 per cent of those in which reports on the spinal fluid

TABLE VIII
Summary of Case 5 after Patient Came under Author's Care

Date	Blood, Wasser- mann	Wasser- mann	Nonne	Spinal Fluid		Colloidal Benzoin	Treatment
				Cells per Cubic Milli- meter			
8-11-26	33	4411-	+	45		000 000 332 300 000	Arsphenamine (2.3 gm.) (6) Mercuric succinimide (0.2 gm.) (18) Sodium iodide (11 gm.) (17) Intraspinal in- jections (3) Mercurial in- unctions (40)
2- 4-27	—	—	+	13		000 000 331 000 000	Arsphenamine (2.2 gm.) (6) Mercuric succinimide (0.23 gm.) (21)
9- 1-27	—	—	+	5		001 000 021 100 000	Arsphenamine (1.9 gm.) (5) Mercuric succinimide (0.15 gm.) (16) Sodium iodide (3.0 gm.) (9) Bismuth (at home) (35) Inoculation Malaria
2- 3-28	44	4421-	+	22*		033 103 333 100 000	
9-18-28	21	21- - -	—	3† 2		002 003 331 000 000	Arsphenamine (1.9 gm.) (6) Mercuric succinimide (0.22 gm.) (20) Bismuth (at home) (15)
4- 4-29	—	—	—	3		121 003 311 000 000	Arsphenamine (1.8 gm.) (6) Bismuth (1.2 gm.) (12)
10-18-33	—	—	—	1		000 000 331 000 000	No treatment

* Small lymphocytes.

† Large lymphocytes.

had indicated only mild or moderate involvement, whereas among cases in which the formula of the spinal fluid was of paretic type, in only 30 per cent was there a reversal to negative. When it was observed that the results from malaria therapy alone were unsatisfactory at the end of the first year, arsphenamine and mercury or bismuth again were given intensively. In other words, if favorable results from malaria treatment were lacking at the end of six or twelve months, intensive specific antisyphilitic measures were instituted in an effort to ward off the appearance of parenchymatous changes in the nervous system.

The absence of serologic relapse was one of the outstanding features of this study. In only one case did I find a relapse to positivity of the spinal fluid after a negative report had been obtained following malaria treatment. Death occurred in one case, the cause for which could not be found at necropsy.

Fever treatment by the newer electrical devices has also been tried in a few cases, but sufficient time has not as yet elapsed to allow deductions to be made in regard to this method of treatment.

Ample evidence is now at hand to allow the assertion that asymptomatic neurosyphilis is the forerunner of dementia paralytica or tabes dorsalis. Also, it is an acknowledged fact that in many cases of asymptomatic neurosyphilis a satisfactory serologic response follows intensive application of the so-called specific remedies. However, this study further emphasizes the fact that those patients who fail to derive serologic reversal from specific agents are entitled to the benefit of malaria therapy because, on a basis of comparative percentages, malaria therapy is more valuable in the prevention of parenchymatous neurosyphilis than it is in the treatment of it.

BIBLIOGRAPHY

1. CLARK, T., PARRAN, T., JR., COLE, H. N., MOORE, J. E., O'LEARY, P. A., STOKES, J. H., and WILE, U. J.: Coöperative clinical studies in the treatment of syphilis. Reprint No. 41, from Venereal Disease Information, U. S. Public Health Service, 1932, xiii, 13-14.
2. MOORE, J. E.: The modern treatment of syphilis, 1933, Charles C. Thomas Company, Baltimore.
3. O'LEARY, P. A.: Treatment of neurosyphilis by malaria; serologic results and a comparison with treatment by typhoid vaccine, Jr. Am. Med. Assoc., 1928, xci, 543-544.
4. O'LEARY, P. A.: Treatment by malaria in asymptomatic neurosyphilis, Jr. Am. Med. Assoc., 1931, xcvi, 1585-1586.
5. O'LEARY, P. A., and RUBENSTEIN, M. W.: A study of acquired syphilis in family groups, Minnesota Med., 1928, xi, 406-409.

CONGENITAL CYSTIC DISEASE OF THE LUNGS *

CASE REPORTS

By LEWIS J. MOORMAN, M.D., F.A.C.P., *Oklahoma City, Oklahoma*

THE first report on congenital cystic disease of the lungs in the American literature was made by Koontz ¹ in 1925. In Europe Pappenheimer ³ had reported his study of a museum specimen as early as 1912. Following Koontz's article further cases have been reported in this country by Wood and Garvin,² Robert Miller, Jr.,⁴ Eloesser,^{5, 6, 7} Moore,⁸ Lehnhoff,⁹ Swanson, Platou and Sadler,¹⁰ Lilienthal,¹¹ Gibson,¹² Tillotson,¹³ Parmelee and Apfelbach,¹⁴ Stewart, Kennedy and James,¹⁵ Nelson,¹⁶ Cabot,¹⁷ Pollock and Marvin,¹⁸ Wolman,¹⁹ Anspach and Wolman,²⁰ Croswell and King.²¹ The reported American cases now number 30.

These 30 cases fall roughly into two age groups. Eleven cases were found in infants, the clinical features which attracted attention being attacks of dyspnea and cyanosis with ultimate respiratory failure. The remaining cases (with the exception of one stillborn case ¹⁹ and two or three cases occurring in later childhood or adolescence) were all discovered in patients between the ages of 20 and 60 years. In this adult group the predominant clinical symptoms were persistent or recurring attacks of cough, expectoration, dyspnea and cyanosis. In addition the occurrence of pain in the chest, hemoptysis, and of febrile attacks is reported in several cases.

A study of the data of these 30 cases suggests that 16 were instances of polycystic disease while 14 were apparently cases of solitary cyst.

In 1925 Koontz ¹ published with his case report a careful review and analysis of 108 European cases. These cases ranged in age from one day to 84 years, five cases being reported as stillborn. Forty-five were males, 38 females, and the sex of 25 was not mentioned. The disease was unilateral in 72 instances and bilateral in 27; in nine the site of the disease process was not reported. Of the 72 unilateral cases, 47 were in the left lung and 25 in the right.

While the clinical data were very incomplete, the following were among the predominant symptoms: cough, expectoration, dyspnea, cyanosis, and periodic febrile attacks with exacerbation of the above symptoms. Symptoms, however, were not uniformly present, since many of the reported cases were first discovered at autopsy or by roentgen-ray examinations. The most common cause of death was pneumonia. A number of cases had died in infancy or early childhood because of intrathoracic pressure with marked dyspnea and cyanosis. This condition is brought about by respiratory inflation of the cysts through valve-like communications, which cause retention of the inspired air.

* Received for publication February 27, 1934.

In Koontz's paper the available pathological data on each of the 108 European cases have been assembled. A careful study of these brief, yet fairly complete notes indicates that 51 of the cases are classified as congenital polycystic disease, and 31 were reported as congenital bronchiectasis, or atelectatic bronchiectasis. Solitary cyst was reported in 16 cases. In the 10 remaining cases various congenital cystic and non-cystic conditions are reported which apparently should not be classified as congenital cystic disease of the lungs.

DIAGNOSIS

It is evident from the literature reviewed above that the clinical picture in congenital cystic disease of the lungs may be a very complex one, offering grave diagnostic difficulties.

Among the factors which may influence the clinical picture are: the question of whether the cysts do or do not communicate with a bronchus, since closed cysts may contain fluid; the question, in cysts that do communicate with a bronchus, whether there is a valve-like action in the narrow bronchus which results in inflation of the cyst with consequent pressure effects; the extent of pressure-atelectasis of the non-cystic lung tissue due to encroachment of the cysts, and the presence or absence of secondary infection leading to pleural adhesions, areas of pneumonitis, bronchiectasis, etc.

If the cysts do not communicate with the bronchi, or if there is free communication without secondary infection there may be no symptomatic evidence of the disease. If the cysts and the bronchi communicate, with valve-like constrictions at the point of communication, distressing and even fatal dyspnea and cyanosis may develop. In other cases escaping early fatal intrathoracic pressure, the symptoms may range from those representing a mild bronchitis to those found in cases of advanced pulmonary tuberculosis, or in non-tuberculous suppurative pulmonary infections. With such a marked variation in clinical and pathological manifestations, one may expect the physical signs to cover a correspondingly wide range. Roentgen-ray studies present similar diagnostic difficulties.

The differential diagnosis must begin with intracranial and intrathoracic birth injuries and end with the respiratory affections of old age. In infancy, thymic syndrome and congenital pulmonary atelectasis are to be considered. In later life congenital cystic disease must be differentiated from pulmonary tuberculosis; non-tuberculous pulmonary infections including pulmonary abscess and bronchiectasis; massive pulmonary atelectasis; congestive heart failure; other types of intrathoracic cysts; spontaneous pneumothorax; intrathoracic new growths; diaphragmatic hernia; and possibly from foreign bodies in the bronchi.

The above conditions enter the field of differential diagnosis, chiefly because of the varied clinical and pathological manifestations possible in the course of congenital cystic disease of the lungs. While space will not

permit a separate consideration of each condition with which this disease may be confused, it may be useful to call attention to certain of the chief diagnostic features of this condition which are to some extent distinctive.

First, the history of the case may yield valuable diagnostic data. The existence of cough, dyspnea and cyanosis from the time of birth or for at least a period of years, plus a history of periodic exacerbations of the respiratory symptoms and signs, should lead one to suspect the possible presence of congenital cystic disease. Repeated sputum examinations negative for tubercle bacilli support the above suspicion. Such a history, supplemented by a careful physical examination, will considerably narrow down the number of diagnostic possibilities. A careful study of good stereo roentgen-ray films may yield decisive diagnostic information. In case polycystic disease of the lungs is present, even though there may be areas of opacity as a result of atelectasis and associated infection, the films may reveal a designless net-work with graceful lines falling across large areas, practically devoid of lung markings. These fine lines do not correspond in location, direction, or in general appearance to the uniform tracings of the normal bronchial tree; nor to those occasionally appearing as a result of thickened pleura in the interlobar fissures. Neither do they have the appearance of the well defined shadows occasionally produced by thin-walled tuberculous cavities. The mediastinal structures may be undisturbed or they may be displaced toward the affected side through the influence of atelectasis, fibrosis and pleural adhesions, or in the opposite direction through over-distention of the cysts.

The above described picture may be considered pathognomonic of open polycystic degeneration of the lung. In doubtful cases bronchoscopic exploration and lipiodol injections followed by roentgen-ray studies may be of material aid. If the pleural cavity is not obliterated by adhesions, artificial pneumothorax may supply definite diagnostic data.

In case the cysts do not communicate with the bronchi, they may, or may not, contain fluid. The diagnosis of fluid-containing congenital cysts may require the elimination of dermoid and echinococcic cysts and new growths. Dermoid cysts may often be definitely identified by sufficient roentgen-ray penetration to discover the presence of opaque contents such as teeth, bone and cartilage. The present available specific diagnostic procedures should determine the presence or absence of echinococcic cysts. Diaphragmatic hernia admitting portions of stomach and intestines to the thoracic cavity, may be differentiated by the presence of intrathoracic borborygmi and by roentgen-rays following an opaque meal. In the instances of circumscribed pneumothorax and of new growths, a period of observation will usually disclose changes which will assist in differentiating these conditions from congenital cystic disease.

PATHOGENESIS

The pathogenesis of congenital pulmonary cysts has received much consideration without consensus of opinion. Architectural and histological studies indicate that the majority of such cysts are bronchogenic in character; others are reported as being lymphangiomatous and still others reveal their origin by the presence of a lining of gastric or esophageal mucosa. Anspach and Wolman²⁰ believe that all congenital air cysts are fluid-filled cysts at birth. In their opinion, the transformation is post-natal and may be followed by the kaleidoscopic clinical course pictured above. They assume that the cysts rupture into the bronchi and that the escaping fluid is swallowed as it is replaced by inspired air. A study of the reported stillborn cases tends to support this teaching.

TREATMENT

The distressing attacks of dyspnea and cyanosis, often occurring soon after birth, may be relieved through equalization of intrathoracic pressure by introducing a needle into the inflated cyst, or cysts. Though this is not free from hazards, it may relieve symptoms and prolong life while more radical surgical procedures are being considered. When possible, the introduction of a needle for the relief of intrathoracic pressure should be assigned to someone experienced in the use of artificial pneumothorax. This is important because the patient's interests may be safe-guarded by a practical knowledge of intrathoracic phenomena as expressed through manometric readings.

Symptom-free cases accidentally discovered, should be closely observed and periodically checked through the study of serial roentgen-ray films. The treatment of other cases surviving the period of infancy should be planned according to the exigencies of the individual case. Those resembling advanced pulmonary tuberculosis or extensive pulmonary suppurative infections, and manifesting persistent progressive symptoms and signs, should be carefully studied with a view to surgical management. The surgical measures of choice and the successive surgical steps will depend upon the clinical condition of the patient, and the character, extent, and location of the pathologic lesions.

CASE I

R. W. B., white male, aged 28. First examined on 6/3/32. *Chief complaints:* fever, productive cough, shortness of breath and loss of strength.

Family History: Negative. Married nine years, wife and three children in good health. Past personal history uneventful except as it relates to the present illness.

Present Illness: The patient has had shortness of breath and paroxysmal attacks of coughing for as long as he can remember. About three weeks before coming for examination, he became acutely ill with fever and chilly sensations. These symptoms were accompanied by increased cough and expectoration and by loss of strength.

Supplementary history obtained from patient's mother indicates that he had an attack of fever at eight years of age which was diagnosed as bronchopneumonia and

lasted for about six months. He lost weight and strength, and the attending physician evidently suspected tuberculosis. He has suffered from similar attacks two or three times each year until three years ago. Though he continued to cough and expectorate quantities of sputum, this is the first acute attack in three years.

Physical Examination: A man of small stature, moderately overweight. Skin and mucous membranes pale, suggesting secondary anemia. There was obvious dyspnea and slight cyanosis. Temperature 101, pulse 144; respiration 36; blood pressure 95 mm. of Hg systolic and 70 diastolic.

The further examination was essentially negative aside from the examination of the lungs which revealed a classical picture of advanced pulmonary tuberculosis of the right lung with multiple cavities. Signs of the latter predominated over the upper half of the right thorax. There was marked dullness at the right base; it was thought that the right diaphragm occupied a relatively high position and was apparently immobile. There were a few medium crackling râles in the lower half of the left lung. The heart and trachea were displaced toward the right. All these phenomena were considered rather typical of chronic ulcerative pulmonary tuberculosis with thickened adherent pleura and possibly atelectasis.

The first stereo roentgen-ray films (figure 1 *A*) were reported as follows: "Roentgen examination of the chest reveals a very heavy infiltration on the right side around the hilus and reaching down to the diaphragm. Beyond this heavily infiltrated area the chest presents a very peculiar appearance as if it were filled with bubbles. Laterally and above the hilus region these so-called bubbles are intermixed with some heavy, irregular shadows. The trachea is pulled toward the right side. The point of bifurcation can be very definitely located at a point at least one-half inch to the right of the margin of the spine.

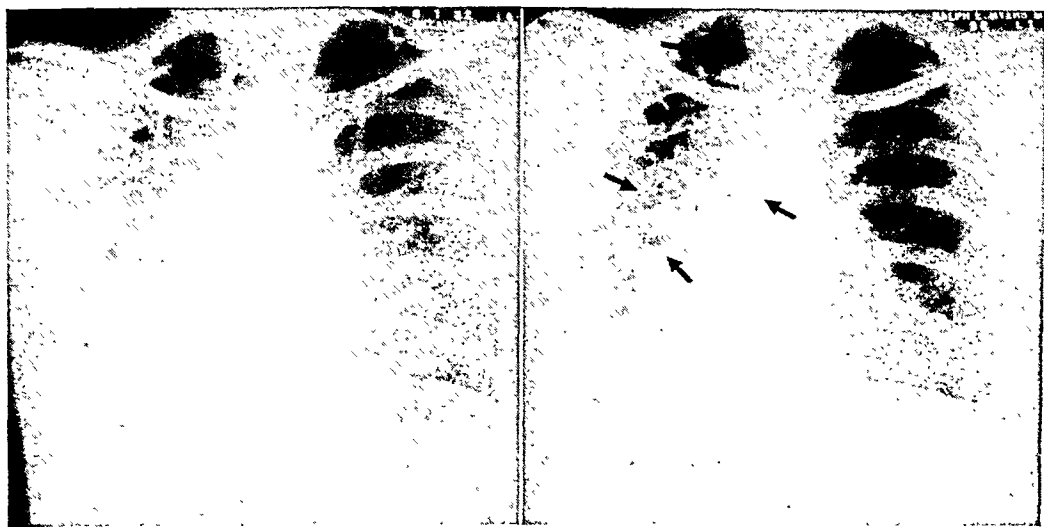


FIG. 1 *A* and *B* (Case 1). In this picture *A* represents a film made on 6/1/32. Note the heavy infiltration in the lower half of right lung with irregular tracings immediately above, also absence of tracing at apex. There is moderate infiltration toward the base of left lung. The heart and trachea are obviously displaced toward the right. *B* represents a film made 7/2/32, two weeks after right phrenicectomy. Note the rather marked reduction in the opacity both right and left. There is no change in the position of mediastinal structures.

"The left hilus shadow is very broad and heavy. Extending outward and downward from this is a heavy, mottled infiltration which reaches out in quite close proximity to the periphery. The upper third of the left chest shows a heavy peribronchial

infiltration, but is fairly clear in comparison with the lower part. Left dome of the diaphragm is regular in outline. *Diagnosis:* Active tuberculosis (far advanced)."

This interpretation is interesting in that it definitely describes the polycystic degeneration, yet reports a diagnosis of "active tuberculosis, far advanced." The tentative clinical diagnosis was advanced pulmonary tuberculosis. Though the unusual roentgen-ray findings were puzzling, the patient was admitted to the Farm Sanatorium as a case of pulmonary tuberculosis.

Repeated negative sputum examinations led to further doubt and the diagnosis was changed to that of nontuberculous pulmonary infection with unusual bronchiectatic, of cystic, cavities. The marked displacement of mediastinal structures toward the affected side was attributed to pulmonary atelectasis and fibrosis resulting from the long continued mixed infection. Careful examination of the sputum for fuso-spirochetal types of organisms proved negative. Sputum cultures and guinea pig inoculation failed to yield diagnostic data.

While resting in bed the patient's temperature ranged from 97° to 101°, the pulse rate from 80 to 132. He raised six to eight ounces of sputum daily.

After two weeks' observation, collapse therapy was advised. Artificial pneumothorax was impossible because of pleural adhesions; a right phrenicectomy was done June 16. As a result of phrenicectomy, there was a 50 per cent reduction in cough and sputum. Complete thoracoplasty was advised but was refused by the patient ostensibly because of a desire to change climate. The patient remained under observation until July 26, 1932.

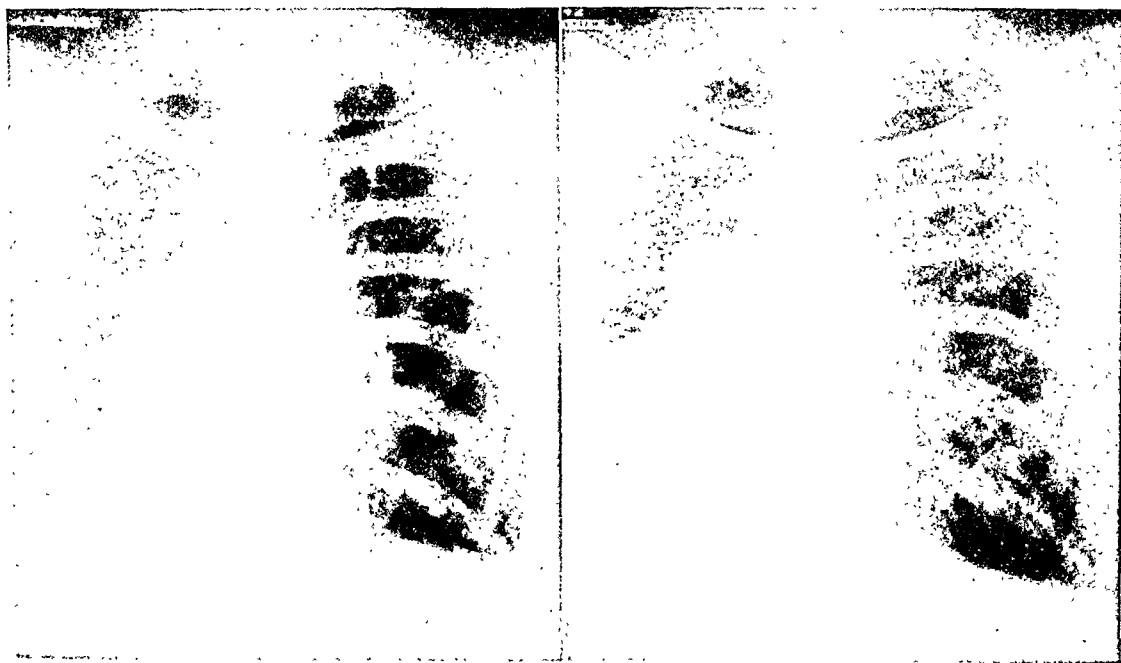


FIG. 2 *A* and *B*. (Case 1.) *A* represents a film made 7/27/32. Note further clearing of opacity in right lung, also in lower left. *B*, made 11/14/33, shows further clearing of opacity and the more obvious irregular tracings throughout the right lung. The right diaphragm is elevated. The position of mediastinal structures is unchanged.

Stereo films made two weeks after phrenicectomy (figure 1 *B*) revealed some decrease in the density of the infiltrated areas with resulting accentuation of the polycystic condition.

Several months after the patient passed from our observation, the report of Wood and Garvin² prompted a review of the roentgen-ray films and led to a diagnosis of congenital polycystic disease of the right lung.

August 29, 1933, the patient returned for examination. He gave a history of having been in Colorado during the interval of approximately 13 months. Cough and expectoration had gradually grown less; he had escaped acute febrile attacks and his general condition was much better.

Upon examination it was obvious that he was somewhat less cyanotic and dyspneic. There was less evidence of moisture in the right lung, though signs of cavity formation were widely evident. In the mid-zone of the right chest there was a distinct whistling sound usually audible only upon expiration. This was probably due to air being forcibly expelled through a constricted or valve-like bronchial communication. The râles formerly present at the base of the left lung had disappeared. The right diaphragm was elevated and immobile. Apparently phrenicectomy had accomplished a great deal of good and in view of the marked improvement, thoracoplasty was not again advised.

The roentgen-rays in figure 2 are reported through the courtesy of Dr. G. Burton Gilbert of Colorado Springs. They indicate rather marked diminution in the infiltration in the lower half of the right lung, and also further clearing of the left lung. These findings are in keeping with the history and clinical manifestations reported above.

CASE II

P. C., admitted to St. Anthony's Hospital February 3, 1928, white male, aged 33, single.

Family History: Apparently negative. Past personal history uneventful.

Present Illness: About two months before the patient first noticed shortness of breath with gradual loss of voice. Because of the progressive hoarseness with both inspiratory and expiratory difficulty, laryngeal diphtheria was suspected and antitoxin given. There was no response to this treatment and after two months of increasing dyspnea and hoarseness, the patient was referred to Dr. R. M. Balyeat, of Oklahoma City, for diagnosis and treatment. The author is indebted to Dr. Balyeat for the privilege of seeing this case in consultation.

A further study of the history indicated that the patient had lost 15 or 20 pounds in weight and that he had suffered from a gradual increase in cough with the expectoration of quantities of mucoid material.

Physical Examination: Essentially negative except for those symptoms and signs referable to the thorax. The temperature was normal, pulse 86, and the blood pressure 110 mm. of Hg systolic and 80 diastolic. There was apparently some obstruction to both inspiration and expiration. The expiratory phase was prolonged. Expansion of both halves of the thorax seemed to be considerably limited; however, there was apparently some retraction of the right thorax with relative enlargement of the left.

Percussion revealed rather marked dullness over the mid-zone of the right chest with hyperresonance over the whole of the left. It was impossible to outline the normal cardiac dullness, the heart apparently being displaced to the right. There was both visible and palpable evidence of deviation of the trachea to the right.

Auscultation revealed numerous medium and coarse crackling râles over the right lung and a few similar râles at the base of the left. The breath sounds over the right side were very harsh with a low pitched tubular element. The heart sounds were apparently clear but were heard with maximum intensity to the right of the sternum.

A roentgen-ray of the chest (figure 3 A) showed areas of opacity of varying density throughout the right lung, giving the impression that the lung was extensively infiltrated and contained multiple cavities.

The left lung was approximately normal in appearance except that the hilum shadow was moderately heavy and contained a few calcified nodes. The trachea was greatly distorted and displaced to the right. At the point of maximum deviation the

proximal wall of the trachea was at least an inch and one-half to the right of the mid-line.

The heart and great vessels were also markedly displaced to the right and obscured by the general opacity.

Laboratory findings were essentially negative except for a four plus positive blood Wassermann. Sputum examinations were negative for tubercle bacilli and revealed practically nothing but mucus.

The patient remained in St. Anthony's Hospital approximately three weeks. During this time his temperature ranged from 97° to 99°. His respiratory rate varied from 18 to 32, and his pulse from 84 to 120.

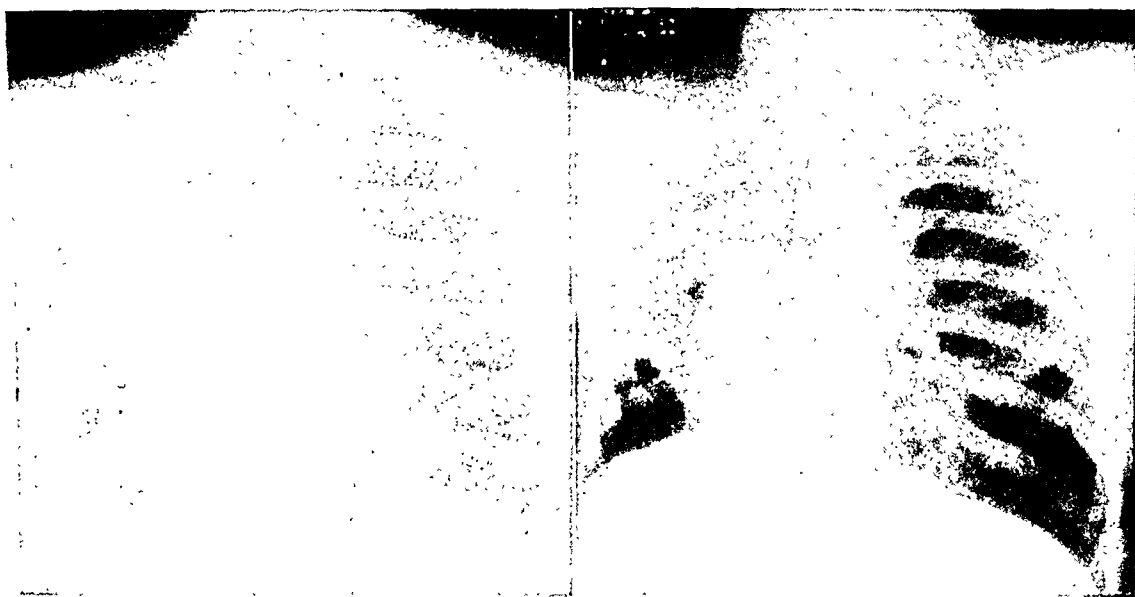


FIG. 3 *A* and *B*. (Case 2.) *A* represents a film made 2/3/28. Note the marked opacity or irregular density throughout the right lung. Also the extreme displacement of heart and trachea toward the right. *B* represents a film made 10/1/33. Note the obvious clearing of the right lung with evidence of cystic formation, especially at the right base. The position of heart and trachea are virtually unchanged.

He was placed on routine anti-luetic treatment and during his three weeks' stay in the hospital he manifested rather marked improvement, with reduction in cough and expectoration, and also some improvement in the dyspneic condition. On account of the presence of a four plus blood Wassermann, the encouraging response to anti-luetic treatment and our inability to make a definite diagnosis of the pulmonary condition, the lesions in the lung were considered as possibly luetic in origin.

Dr. Balyeat's records show that the patient was still under observation on October 4, 1928. He resumed his occupation as foreman of a pipe line crew a few months after leaving the hospital but was not wholly free from symptoms. A recent follow-up by means of a questionnaire indicates that the cough and expectoration disappeared and that the patient is following his usual occupation. The evidence also indicates that the antisyphilitic treatment was faithfully followed.

A recent roentgen-ray of the chest compared with the one made in 1928 (see figure 3 *B*) indicates marked reduction in the opacity on the right side with areas apparently free from lung markings. The largest of these areas seen at the base of the right thoracic cavity suggests the possibility of a circumscribed pneumothorax.

Since he has never had induced pneumothorax, and has had no recent symptoms suggesting spontaneous pneumothorax, it seems reasonable to attribute this finding

to cystic disease. The late appearance of symptoms does not preclude the possibility of congenital cystic disease.

A careful comparison of the two pictures reveals little, if any, change in position of the heart and mediastinal structures. This tends to support the diagnosis of congenital polycystic disease.

While we must accept the diagnosis of syphilis in this case, such a diagnosis does not necessarily explain the intrathoracic pathology. Proved syphilis of the lungs is obviously very rare. In the cases so diagnosed, the pathologic lesions as revealed by roentgen-ray studies do not closely resemble those found in the case under consideration. Neither does the roentgen-ray evidence of lung syphilis persist after treatment such as this case received. The rapid disappearance of roentgen-ray evidence in the diagnosed cases has been considered as diagnostic confirmation.

After careful consideration of the above facts, and taking into account the marked similarity of the main clinical and pathological features in this case and in the one first reported, it seems reasonable to consider this a true case of congenital polycystic disease of the right lung.

CASE III

White female, aged 22. (This case is being reported through the courtesy of Dr. J. A. Myers of Minneapolis.)

History: There is a history of repeated attacks of pneumonia, also of an attack of influenza in 1920. In May 1921, she developed a persistent cough, foul purulent sputum, and fatiguability. On March 9, 1922, the first roentgen-ray film was made (figure 4 *A*).

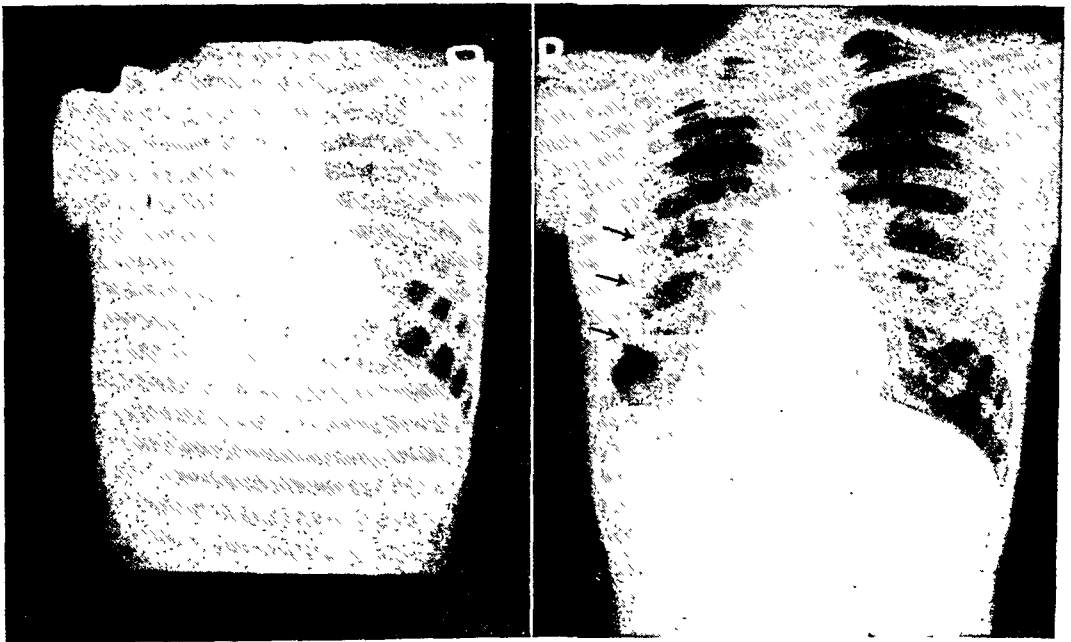


FIG. 4 *A* and *B*. (Case 3.) *A*, under date of 3/9/22, reveals evidence of extensive pathology in the right lung with widespread infiltration. *B* represents a film made 9/21/32 and is remarkable in that the opacity has almost completely disappeared, making more obvious the characteristic markings of congenital polycystic disease.

The interpretation of this film was as follows: "Extensive fibroid pulmonary tuberculosis involving the right lung with extensive cavity formation in the right

upper half of the lung field. There is a marked thickening of the pleura over the entire right chest."

Following this, she was not seen by Dr. Myers or members of his staff for a period of approximately 10 years. When again seen, investigation showed that she had continued to cough and to bring up a moderate amount of foul sputum.

The roentgen-ray diagnosis in 1922 was pulmonary tuberculosis; the subsequent history is suggestive of pulmonary abscess, and yet the patient had passed from childhood to maturity without disaster. Such a course is not in keeping with either advanced pulmonary tuberculosis or pulmonary abscess with extensive pneumonitis. Pulmonary abscess with multiple cavities is particularly prone to prove fatal or to resist all forms of treatment. The latter course is accompanied by roentgen-ray evidence of increase in the pathologic lesions.

The second roentgen-ray film, 9/21/32, presents a surprising picture (figure 4 B). It certainly does not conform to that usually found after 10 years of advanced tuberculosis or pulmonary abscess. Careful examination reveals a remarkable degree of clearing throughout the whole of the right lung field. In the lower half of the right thorax, there are three superimposed circular shadows which are fairly typical of congenital polycystic disease. About the time the second film was made phrenicectomy was performed without material benefit.

In summing up the clinical evidence in this case it should be remembered that there was a history of repeated respiratory attacks during childhood with ultimate development of persistent pulmonary symptoms and signs.

In the light of our present knowledge, the roentgen-ray findings in this case, supplemented by a respiratory history such as that reported, seem to justify its inclusion in this series as a genuine case of congenital polycystic disease of the lungs.

BIBLIOGRAPHY

1. KOONTZ, A. R.: Congenital cysts of lung, *Bull. Johns Hopkins Hosp.*, 1925, xxxvii, 340-361.
2. WOOD, H. G., and GARVIN, R. O.: Congenital polycystic disease of lungs: report of case, *Proc. Staff Meet. Mayo Clin.*, 1933, viii, 176-178.
3. PAPPENHEIMER, A. M.: Congenital cystic malformation of the lung, *Proc. New York Path. Soc.*, 1913, xii, 193-202.
4. MILLER, R. T., JR.: Congenital cystic lung, *Arch. Surg.*, 1926, xii, 392-405.
5. ELOESSER, L.: Congenital cystic disease of lung, *Surg. Clin. N. Am.*, 1928, viii, 1361-1373.
6. ELOESSER, L.: Congenital cystic disease of lung, *Surg., Gynec. and Obst.*, 1931, lii, 747-758.
7. ELOESSER, L.: Congenital cystic disease of lung, *Radiology*, 1931, xvii, 912-929.
8. MOORE, W. F.: Multiple cysts of lung, *Ann. Otol. Rhin. and Laryng.*, 1927, xxxvi, 263-269.
9. LEHNHOFF, H. J.: Pulmonary cysts, *Nebraska Med. Jr.*, 1927, xii, 447-449.
10. SWANSON, W. W., PLATOU, E. S., and SADLER, W.: Congenital cyst of lung, *Am. Jr. Dis. Child.*, 1928, xxxv, 1024-1031.
11. LILIENTHAL, H.: Cyst of lung; recovery following operation for permanent drainage, *Arch. Surg.*, 1929, xviii, 292-299.
12. GIBSON, D. N.: Congenital cystic lung; case report, *Am. Jr. Roentgenol.*, 1929, xxii, 155-157.
13. TILLOTSON, R. S.: Congenital cystic disease of lung; report of case, *Calif. and West. Med.*, 1929, xxxi, 420-422.
14. PARMELEE, A. H., and APPELBACH, C. W.: Congenital air cyst of lung, *Am. Jr. Dis. Child.*, 1931, xli, 1380-1388.
15. STEWART, H. L., KENNEDY, P. J., and JAMES, A. E.: Congenital cyst of lung, *Arch. Path.*, 1932, xiv, 627-636.

16. NELSON, R. L.: Congenital cystic disease of lung; report of case, *Jr. Pediat.*, 1932, i, 233-238.
17. CABOT, R. C.: Cyst of lung with rupture into pleural cavity, *New Eng. Jr. Med.*, 1932, ccvii, 146-148.
18. POLLOCK, W. C., and MARVIN, H. P.: Congenital cystic disease of lung, *Am. Rev. Tuberc.*, 1933, xxvii, 59-66.
19. WOLMAN, I. J.: Case of congenital cystic lung in stillborn fetus, *Bull. Ayer Clin. Lab. Pennsylvania Hosp.*, 1930, ii, 49-54.
20. ANSPACH, W. E., and WOLMAN, I. J.: Large pulmonary air cysts in infancy, with special reference to pathogenesis and diagnosis, *Surg., Gynec. and Obst.*, 1933, lvi, 635-645.
21. CROSWELL, C. V., and KING, J. C.: Congenital air cyst of lung, *Jr. Am. Med. Assoc.*, 1933, ci, 832-834.

MILD HYPOTHYROIDISM *

By RALPH M. WATKINS, B.S., M.D., *Cleveland, Ohio*

INTRODUCTION

THIS modest study represents the combined and correlated symptom findings of a series of 50 patients suffering with mild hypothyroidism.

It is presented with the opinion that the disease or condition or syndrome (for it probably is not a specific disease) is comparatively common. It must be overlooked often. Only two or three years' time has been necessary for me to study these and some other cases in private practice, and any disease picture which is encountered so frequently cannot be rare.

The name mild hypothyroidism is very possibly a misnomer. The thyroid is unquestionably deficient in its action, but other bodily structures also, notably the other endocrine glands, can often be proved to be abnormal in function. The association of inactivity of the thyroid gland with systemic diseases such as low grade infections, cardiovascular-renal disease, deficiency diseases, various anemias and so forth, is so well known as to need no comment. In this study the attempt has been made to avoid reporting any case history in which such afflictions as the above occur.

My view of the matter is this: There are many people, mostly women from 30 years of age onward, who present a vague, uncharacteristic, indefinite train of symptoms and signs, associated with moderate lowering below normal of the basal metabolic rate. Their ailments often are not clearly recognized, but they respond in a reasonably satisfactory manner to the administration of thyroid extract, with or without other glandular substances, plus simple hygienic medical regulations. I feel sure from my experience that non-glandular therapy alone does not relieve them.

I should like to stress particularly the following facts:

1. The clinical picture of mild hypothyroidism is vague.
2. It is often unrecognized.
3. It is often encountered.

RÉSUMÉ OF FINDINGS

In this group 84 per cent were females and 16 per cent males. Two children are included—a girl of 11 and a boy of 12. The latter, by the way, had the lowest metabolic rate of all the group (minus 40 per cent) and yet did not have the picture of true myxedema. The average age of the women was 33.4 years and of the men 35.4 years. The average metabolic rate of the 50 patients was minus 14.3 per cent.

In establishing the basal metabolic rate at the beginning of treatment, from one to five tests were made on each patient. The average for the

* Received for publication January 31, 1934.

whole group is between two and three tests. All the tests were made on the same apparatus and nearly all by the same technician. It seems to me that if only one basal metabolic test is made on a patient there is a definite chance of error because of transitory abnormal conditions of the patient or of the apparatus. I believe that it is better to do at least two, or preferably three, tests over a week's period, and to average the results, before coming to a decision as to the actual basal rate.

It is worth noting that, with few exceptions, the patients were of high intelligence. None was actually impoverished; many had a fair proportion of luxuries; several did responsible work.

A compilation of the symptoms reported by the patients showed that they had occurred in the following proportions:

1. Weakness, loss of muscle strength, abnormal fatigue in 54 per cent.
2. Loss of energy and of initiative in 82 per cent.
3. Nervousness in 86 per cent.
4. Increasing weight in 52 per cent; decreasing weight in 10 per cent.
5. Abnormal dryness of skin and hair in 56 per cent.
6. Menstrual disturbance in $37\frac{1}{2}$ per cent. Of these, about half had gone through the menopause and the rest had a menstrual flow scantier than normal. One patient had menorrhagia.
7. Abnormal desire for sleep in 28 per cent. Unusual wakefulness in 6 per cent.
8. Mental apathy in 40 per cent.
9. Constipation in 44 per cent.
10. Abnormal gaseous eructations in 50 per cent.
11. Headaches in 20 per cent.

Physical examinations brought out the following pertinent points:

1. Overweight averaging 16.1 per cent in 54 per cent of the patients.
2. Underweight averaging 12.8 per cent in 26 per cent of the patients.
3. Normal weight in 20 per cent.
4. The thyroid gland was not enlarged in 76 per cent of the patients. Colloid goiter was present in 14 per cent, and adenomatous goiter in 6 per cent. The thyroid gland had been resected in 4 per cent.
5. The tonsils had been removed in 42 per cent; they were obviously infected in 20 per cent and were apparently normal in 38 per cent.
6. Blood pressure was below normal in 10 per cent, above normal in 4 per cent, and within normal limits in 86 per cent.
7. The pulse rate was abnormally rapid in 52 per cent, unusually slow in 4 per cent, and within normal limits in 44 per cent.
8. One hundred and twenty basal metabolic tests were carried out to establish the rates at the beginning of treatment of the 50 patients. As noted above, the average for the series was minus 14.3 per cent.
9. Associated diseases are common in hypothyroidism and unquestionably play a definite part in it at times. Fifty-two per cent of these pa-

tients had such ailments. In the group, infected sinuses, infected tonsils, dental sepsis, chronic colitis, chronic arthritis, cardiovascular-renal disease each occurred in from three to 10 instances; migraine, chronic bronchitis, phlebitis, essential hypertension, mild diabetes mellitus, endocervicitis, chronic cystic mastitis, chronic oöphoritis, prostatitis and kidney infections occurred each once or twice. I have related this for the purpose of pointing out the susceptibility of these patients to various diseases.

Study of the past histories of these patients was interesting:

1. Sixty per cent had suffered some potentially serious disease earlier in life. Ten patients had had tonsillitis, five pneumonia, five typhoid fever; there were two instances each of hyperthyroidism, cholecystitis, pulmonary tuberculosis, bronchitis, otitis media, pyelitis, phlebitis, pleurisy, and influenza. In single instances the patients reported that they had suffered in the past with colitis, migraine, pyloric stenosis, tuberculous lymphadenitis, appendicitis (without operation), diphtheria and smallpox.
2. Of the 50 patients, 30 were married women. These had had a total of 50 children, a birth rate of 1.67 per married woman.
3. It does not seem possible that there is any other group of patients suffering with a chronic disease which is subjected to so many operations as had been performed in these cases of mild hypothyroidism. Seventy per cent of these patients had undergone surgical operations. There were 26 instances of removal of tonsils or adenoids or both. There were 18 of removal of the appendix. There were scattered reports of removal of the thyroid gland, the uterus, the gall-bladder; a cystic ovary had been removed from one patient and another had been operated upon for tuberculous glands of the neck.

LITERATURE

Lawrence¹ emphasizes abnormal fatiguability of the body as a whole, or subnormal function of any of its parts as suggesting depression of thyroid activity. He goes so far as to state that marked thyroid failure can be present without the development of myxedema.

Weiss and King² remind us that swelling of the eyelids is a comparatively common finding in hypothyroidism and may be the only obvious abnormality of the patient on casual examination.

Warfield³ states that mild hypothyroidism is comparatively common among persons living in goiter regions such as the Great Lakes basin. All classes of people are affected; a considerable proportion are professional men and women. Overweight, underweight or normal weight may be found. He considers the most important single symptom, physical exhaustion which often leads to a neurasthenic state.

Thurmon and Thompson,⁴ in studying this problem, were interested to find at least 11 patients in their series who had basal metabolic rates varying from minus 11 to minus 24 and who had no complaints at all. It was only by careful study in addition to metabolic tests that the diagnosis of hypothyroidism could be maintained.

Youmans and Riven⁵ stress the fact that hypothyroidism without myxedema is a more common condition than is generally appreciated and that it has a wide distribution.

Baskett⁶ finds mild hypothyroidism comparatively common in the Mississippi basin.

Craddock,⁷ Hoge,⁸ and McKean⁹ cite many symptoms of this ailment. These include apathy, senile expression, dry skin and hair, obesity, slow pulse, slow digestion and excretion, feeling of coldness, stiffness and pain in the extremities, mental depression, fatiguability, menstrual disturbances, biliousness, feeling of inertia in the morning and of stimulation in the evening, sluggish memory, difficulty in concentration, headache, slight dyspnea, loss of libido, lowered temperature and blood pressure, a tendency for dental caries to develop, susceptibility to eczema and furuncles, falling hair, obesity in early life, susceptibility to intercurrent infections, nervousness, at times loss of weight, tinnitus, relative sterility, narrowness of the lid slits, lack of appetite, poverty of thought, lack of feeling, clumsiness. The authors state that the ratio of females to males suffering with the disease is about four to one. Laboratory findings are characteristic only in that there is some lowering of the basal metabolic rates, slight increase in the carbohydrate tolerance, mild secondary anemia with slight leukopenia and relative lymphocytosis.

Gordon¹⁰ notes the susceptibility of these patients to mild respiratory infections.

Alexander¹¹ mentions the occurrence of paresthesia and vasomotor rhinitis.

Thommen¹² reports a few obscure cases in which such conditions as menorrhagia, alopecia areata, malnutrition, albuminuria and glycosuria and chronic eczema were relieved by the use of thyroid extract.

McKinlay¹³ reports a case of unexplained secondary anemia cured by adding thyroid extract to the usual treatment.

Brown¹⁴ reports a number of patients with this disease who had a moderate gastric hypoacidity. This is a frequent finding.

Hayward¹⁵ and Woods describe two groups of these patients with regard to mental derangements; one group presented symptoms resembling those of a depressive psychosis and another, symptoms which suggested dementia precox.

Jacobi¹⁶ says that hypothyroidism is able to stir up latent schizophrenia.

Ziegler¹⁷ notes that these people show irritability and frequently hallucinations.

Vis¹⁸ links up the thyroid deficiency with that of other glands and states that the accompanying disorder in the ovaries is responsible for dysmenorrhea; in the adrenals for low blood pressure and dyspnea; in the gonads for impotence and in the parathyroids for tingling and numbness of the fingers.

Barlow¹⁹ pleads for the earlier recognition of thyroid deficiency and has an interesting observation, namely: that in many of these patients the outer one-third of the eyebrows is either gone or scanty, with the remainder of the eyebrows coarse and fan-shaped.

Sloan²⁰ notes mental subnormality following moderate lack of thyroid secretion in fetal life. These children are not necessarily cretins.

Harrell²¹ found in his series 80 per cent of the patients to be suffering from focal infection.

SUMMARY

Fifty patients, mostly females, have been studied for the purpose of demonstrating some of the salient points of mild hypothyroidism. The name of the disease may be incorrect; rather, the condition may be a syndrome in which abnormalities of other organs, besides the thyroid gland, play a part. The condition is frequently present in people of middle age. Evidences of the disease are vague in that there are no specific symptoms. Outstanding in these complaints are the indefinite loss of energy, nervousness, mental apathy, extreme fatigue, loss of muscle strength, general weakness, increase of weight, constipation and so on, of which so many women complain.

The basal metabolic rate is lowered to a point moderately below normal.

There are no characteristic findings on physical examination. Those most frequently discovered are a moderate degree of overweight, rapid pulse, normal blood pressure, unusual dryness of the skin and hair, and frequently various associated diseases usually of chronic type.

It is of some interest to note that a majority of these patients had had an abnormal number of potentially serious ailments in their earlier years.

The average number of children born to the married women of the group was well below that of the race in general.

A strikingly large proportion of these patients had been operated upon for various conditions. It is possible that many of the operations were carried out in an effort to relieve these people of their vague complaints.

CONCLUSIONS

It seems to me fair to state the following facts in regard to mild hypothyroidism:

1. The disease is unquestionably common.
2. The disease often remains undiagnosed or is improperly diagnosed for a long period of time.
3. The disease has no clear cut, specific symptoms or signs.

REFERENCES

1. LAWRENCE, C. H.: Physiological background for symptoms of thyroid failure, with consideration of results of treatment, *Boston Med. and Surg. Jr.*, 1927, cxcvi, 43-50.
2. WEISS, H. B., and KING, C.: Swelling of eyelids in patients with hypothyroidism, *Ohio State Med. Jr.*, 1932, xxviii, 341-343.
3. WARFIELD, L. M.: Hypothyroidism, *ANN. INT. MED.*, 1928, ii, 446-455; *Hypothyroidism*, *Jr. Am. Med. Assoc.*, 1930, xcv, 1076-1080.
4. THURMON, F. M., and THOMPSON, W. O.: Low basal metabolism without myxedema, *Arch. Int. Med.*, 1930, xlvi, 879-897.
5. YOUMANS, J. B., and RIVEN, S. S.: Hypothyroidism without myxedema, *ANN. INT. MED.*, 1932, v, 1497-1505.
6. BASKETT, E. D.: Hypothyroidism in young women, *Jr. Missouri Med. Assoc.*, 1931, xxviii, 355-358.
7. CRADDOCK, A. B.: Hypothyroidism of adults, *South. Med. Jr.*, 1929, xxii, 141-143.
8. HOGE, A. H.: Hypothyroidism; diagnosis and treatment, *West Virginia Med. Jr.*, 1929, xxv, 87-89.
9. MCKEAN, R. M.: Hypothyroidism without myxedema; its recognition and treatment, *Jr. Mich. State Med. Soc.*, 1929, xxviii, 128-131.
10. GORDON, A. H.: Some clinical aspects of hypothyroidism, *Canad. Med. Assoc. Jr.*, 1929, xx, 7-10.
11. ALEXANDER, E. L.: Hypothyroid state, *Virginia Med. Monthly*, 1931, lviii, 107-111.
12. THOMMEN, A. A.: Obscure forms of thyroid insufficiency, *Med. Jr. and Rec.*, 1930, cxxxix, 603-608.
13. MCKINLAY, C. A.: Manifestations of hypothyroidism in limited fields of medical practice, *Minnesota Med.*, 1930, xiii, 281-284.
14. BROWN, T. R.: Effect of hypothyroidism on gastric and intestinal function, *Jr. Am. Med. Assoc.*, 1931, xcvi, 511-513.
15. HAYWARD, E. P., and WOODS, A. H.: Mental derangements in hypothyroidism; their misleading effects in diagnosis, *Jr. Am. Med. Assoc.*, 1931, xcvi, 164-165.
16. JACOBI, E.: Myxödem und Psychose, *Arch. f. Psychiat.*, 1929, lxxxvi, 426-441.
17. ZIEGLER, L. H.: Psychosis associated with myxedema, *Jr. Neurol. and Psychopath.*, 1930, xi, 20-27.
18. VIS, W. R.: Diagnosis of mild hypothyroidism, *Jr. Mich. Med. Soc.*, 1931, xxx, 829-830.
19. BARLOW, H. C.: Plea for earlier recognition of thyroid deficiency, *Practitioner*, 1931, cxxxvii, 648-658.
20. SLOAN, E. P.: Subnormality from hypothyroidism, *Clin. Med. and Surg.*, 1931, xxxviii, 91-96.
21. HARRELL, C. L.: Thyroid deficiency; clinical study, *Virginia Med. Monthly*, 1930, lvii, 71-81.

THE USE OF CALCIUM ORTHO-IODOXYBENZOATE IN THE TREATMENT OF ARTHRITIS, WITH A DISCUSSION OF ITS POSSIBLE VALUE IN SOME OTHER ORTHOPEDIC CONDITIONS *

By THOMAS WHEELDON, M.D., *Richmond, Virginia*

SALTS of ortho-iodoxybenzoic acid have been used clinically in the treatment of arthritis since 1926 when Young and Youmans¹ reported the successful use of ammonium ortho-iodoxybenzoate, given intravenously, in 43 cases. Later Smith² and Cottrell³ reported some success with the oral administration of calcium ortho-iodoxybenzoate, and this rapidly became the route of choice with the medical profession due to the fact that severe general reactions often followed the intravenous use of the ammonium salt.

For two years the writer has been using calcium ortho-iodoxybenzoate as a routine procedure in an investigation comprising a portion of the arthritic cases in his orthopedic practice. This investigation consists of 282 cases. Of these, 236 (Group I) were studied in the usual clinical manner, but complete laboratory and roentgenological study was not possible in every instance. In 46 cases (Group II) the investigation was more complete in that it was possible to analyze them in greater detail with full laboratory findings. These two groups provide a peculiar method for evaluating results, in that the general group (Group I) might be said to show what improvement may be expected in that large mass of arthritic cases seen by the internist or general practitioner and treated by him in the usual manner. The smaller group (Group II), on the other hand, seems to give a more accurate method of judging the real value of the drug in cases which were disciplined to carry out the treatment uninterruptedly.

In visiting a number of rural clinics, geographically separated, it was necessary to find some form of adjuvant drug treatment which the patient could use in safety between visits and which could be counted upon, not only to relieve arthritic symptoms, but also to promote the success of other orthopedic measures (exercises, diet, appliances, etc.) which had been previously initiated.

Not only did calcium ortho-iodoxybenzoate hold out definite promise of curative results, but it also seemed suitable for the following reasons:

1. It is not related to cinchophen or other quinoline derivatives which, when used without close supervision, may cause severe allergic manifestations or hepatic damage.
2. It does not cause addiction in the patient.
3. Only occasionally do patients complain of nausea (less than 3 per cent of over 500 cases) or other gastrointestinal disturbances, following its

* Received for publication February 6, 1934.

ingestion. This agrees with the findings of earlier workers ^{1, 2, 3} who found the drug relatively nontoxic even in massive doses.

4. Apart from the objective improvement effected, it gives the patient a subjective sense of improvement which helps him to continue with his régime.

METHOD OF TREATMENT

A standard treatment is employed for all cases whether seen in clinics or in private practice. This includes removal of foci of infection where discoverable; exercises and apparatus to improve body mechanics; body hygiene to check constipation; proper diet, and local treatment of affected joints. Arthritic vaccine (either autogenous or that made from stock strains) and thyroid extract were given to the occasional case in this series. To some patients, very small stimulating doses of sodium salicylate and potassium iodide were administered, but the majority of cases received no medication other than calcium ortho-iodoxybenzoate,* 2 grams (four tablets of $\frac{1}{2}$ grain each) daily. And here it may be noted that one should not look for any real improvement to manifest itself in less than one month. The use of the drug must be continued for a period of at least 30 days if it is to produce lasting benefit. It was in the case of patients who coöperated best in this respect that the most satisfactory results were obtained.

The following criteria for improvement were used:

<i>Subjective Symptoms</i>	<i>Objective Symptoms</i>
Pain on activity	Deformity
Pain without activity	Size of joints
Tenderness to pressure	Range of motion
Occupational usefulness	Local heat
Emotional stability	Crepitus
Appetite	Condition of tegmentum
Sleep	Improvement of foci
General well-being (as judged by patient's own opinion as to his improvement)	Change in weight

GROUP I (GENERAL STUDY)

Calcium ortho-iodoxybenzoate has been administered, as described above, to a general group (Group I) of 236 arthritic cases treated over the past two years. Practically all of these cases were complicated by general orthopedic conditions such as faulty posture, static deformities of the feet, deformities of the joints, muscle and tendon contractions, etc. Varying degrees of ankylosis or instability of the joints were also present. Most of the patients were ambulatory. The extent of deformity or crippling also spread over a wide range. Treatment previous to this investigation had been varied.

* This was supplied through the courtesy of the Smith, Kline and French Laboratories under the name of Oxo-ate "B."

TABLE I
Analysis of 46 Cases. Group 2

No.	Age	Sex	Duration in Years	Type	Degree	Duration of Use of Drug in Mos.	Improve- ment	Remarks
1	64	F.	3	H	Severe	August 1932-January 1934 (16 mos.)	Marked	No weight reduction effected.
2	64	F.	7	H	Severe	August 1932-January 1934 (16 mos.)	Excellent	Definite hypertension improved.
3	35	F.	2	A	Severe	August 1932-January 1934 (16 mos.)	Startling	Totally incapacitated—back to housework.
4	42	F.	3	A	Severe	August 1932-January 1934 (16 mos.)	Marked	
5	66	F.	10	H	Moderate	August 1932-January 1934 (16 mos.)	Marked	Definite hypertension relieved.
6	25	F.	3	A	Severe	August 1932-January 1934 (16 mos.)	Marked	Manipulation of joints now possible.
7	47	M.	6	H	Moderate	August 1932-January 1934 (16 mos.)	Excellent	Totally disabled—now back at work.
8	65	M.	7	H	Moderate	August 1932-January 1934 (16 mos.)	Marked	Back at work.
9	50	F.	7	H	Severe	August 1932-January 1934 (16 mos.)	Marked	
10	48	F.	5	A	Severe	August 1932-January 1934 (16 mos.)	Marked	Classical deformity of spine corrected.
11	59	F.	10	H	Severe	August 1932-January 1934 (16 mos.)	Marked	Manipulation of joints now possible.
12	50	F.	6	H	Severe	August 1932-January 1934 (16 mos.)	Marked	
13	68	F.	7	H	Severe	August 1932-January 1934 (16 mos.)	Marked	
14	57	F.	3	A	Moderate	August 1932-January 1934 (16 mos.)	None	X-ray shows less calcium in vessel walls.
15	64	F.	7	H	Moderate	August 1932-January 1934 (16 mos.)	Marked	Patient non-coöperative
16	64	F.	7	H	Severe	August 1932-January 1934 (16 mos.)	Marked	Definite hypertension improved.
17	35	F.	3	A	Severe	August 1932-January 1934 (16 mos.)	Marked	Back at work.
18	42	F.	3	H	Moderate	August 1932-January 1934 (16 mos.)	Marked	
19	68	F.	7	H	Severe	August 1932-January 1934 (16 mos.)	Marked	Doing housework again.
20	25	F.	3	A	Moderate	August 1932-January 1934 (16 mos.)	Marked	Now works 14 hours a day.
21	47	M.	7	H	Moderate	August 1932-January 1934 (16 mos.)	Marked	Back at work.

TABLE I (Continued)
Analysis of 46 Cases. Group 2

No.	Age	Sex	Duration in Years	Type	Degree	Duration of Use of Drug in Mos.	Improvement	Remarks
22	60	M.	5	H	Severe	August 1932-January 1934 (16 mos.)	Marked	Classical deformity of spine improved.
23	55	F.	5	H	Severe	August 1932-January 1934 (16 mos.)	Marked	Classical deformity of spine improved.
24	65	F.	5	A	Moderate	August 1932-January 1934 (16 mos.)	Marked	Now self-supporting.
25	55	F.	5	H	Severe	August 1932-January 1934 (16 mos.)	Marked	Decompensated heart condition improved.
26	55	F.	5	H	Severe	August 1932-January 1934 (16 mos.)	Marked	
27	65	F.	8	H	Severe	August 1932-January 1934 (16 mos.)	Marked	
28	55	F.	7	H	Severe	August 1932-January 1934 (16 mos.)	None	
29	59	F.	5	H	Moderate	August 1932-January 1934 (16 mos.)	Marked	
30	60	F.	5	H	Severe	August 1932-January 1934 (16 mos.)	Marked	Doing housework again.
31	35	F.	3	A	Severe	August 1932-January 1934 (16 mos.)	Marked	Doing housework again.
32	48	M.	3	A	Moderate	August 1932-January 1934 (16 mos.)	Marked	Doing housework again.
33	35	F.	3	A	Moderate	August 1932-January 1934 (16 mos.)	Marked	Doing housework again.
34	35	F.	3	A	Severe	August 1932-January 1934 (16 mos.)	Marked	Definite hypertension improved.
35	60	F.	8	H	Moderate	August 1932-January 1934 (16 mos.)	Marked	
36	64	F.	5	H	Moderate	August 1932-January 1934 (16 mos.)	Marked	
37	58	F.	8	H	Severe	August 1932-January 1934 (16 mos.)	Marked	
38	25	F.	3	A	Severe	August 1932-January 1934 (16 mos.)	Marked	
39	48	M.	8	H	Moderate	August 1932-January 1934 (16 mos.)	Marked	
40	62	F.	12	H	Severe	August 1932-January 1934 (16 mos.)	Fair	Doing housework again.
41	50	F.	5	H	Moderate	August 1932-January 1934 (16 mos.)	Fair	Doing housework again.
42	48	F.	5	H	Severe	August 1932-January 1934 (16 mos.)	Marked	Doing housework again.
43	59	F.	10	A	Moderate	August 1932-January 1934 (16 mos.)	Marked	Doing housework again.
44	50	F.	8	H	Severe	August 1932-January 1934 (16 mos.)	Marked	
45	64	F.	7	H	Severe	August 1932-January 1934 (16 mos.)	Marked	
46	57	F.	7	H	Severe	August 1932-January 1934 (16 mos.)	None	

H—Hypertrophic arthritis

A—Atrophic arthritis

Dosage—Standard dosage, 2 grams calcium ortho-iodoxybenzoate daily.

The results may be summarized as follows:

Improvement	Number	Percentage
Marked to excellent	116	50%
Fair to good	86	36%
Slight to none	34	14%

GROUP II (SPECIAL STUDY)

In addition to this general group (Group I), 46 arthritic patients were studied over a period of 18 months with full laboratory records taken at intervals (table 1). These records included a roentgen-ray study of the left hand, left knee and the joint most seriously involved in every case. The writer expects to make a supplementary report of this phase at a later date.

Without wishing to enter into any discussion on the vexed question of nomenclature in arthritis, the writer has divided these 46 cases as follows:

Hypertrophic (degenerative) arthritis.....	32.....	70 per cent
Atrophic (proliferative) arthritis.....	14.....	30 per cent

The average age of the patients was 53 years; the average duration of the disease 5.5 years. There were 40 females and 6 males.

The clinical results may be summarized as follows:

Improvement	Number	Percentage
Good to excellent	41	89%
Fair to slight	2	4.3%
None	3	6.7%

In some of these cases the results were startling—the word is used advisedly. Patients who had been chronic invalids for months or years were restored to useful activity, wage-earning employment or the resumption of household duties. A remarkable feature was the improvement noted in hypertensive and heart conditions. In so far as the action of calcium ortho-iodoxybenzoate is as yet undetermined by the writer, it is felt that the improvement in hypertensive and heart conditions must be attributed more to the improvement in the patient's general well-being. Even so, it may be used as a criterion in summing up the value of the treatment. And here it may be reiterated that this group of patients was very carefully followed and controlled, so the results obtained were more successful than one might reasonably expect to find in the cases selected haphazard or in a general group of patients. Of course, the improvement was not due entirely to the calcium ortho-iodoxybenzoate, but the degree of improvement is measured by a comparison with a similar group of patients who did not receive the drug. This standard of comparison is already in the hands of everyone who is dealing with arthritis.

Where improvement occurred, swelling was reduced as shown by actual measurements of the affected joints, the range of motion was enlarged and the general well-being of the patient was greatly enhanced. The relief of pain was not remarkable. It may be noted that when intense discomfort

is present, calcium ortho-iodoxybenzoate may be given conjointly with salicylates or other analgesic drugs apparently without fear of incompatibility.

LABORATORY FINDINGS

Detailed laboratory tests were conducted on the above 46 patients. The results, while not particularly significant, are given because the writer feels that no preparation should be recommended until any possible untoward effects on the various systems have been investigated. Toxicity studies on other antiarthritic agents have been conducted by the writer.⁴

Test	Percentage Unchanged	Percentage Increased	Percentage Decreased
Blood calcium	26	35	39
Blood sugar	59	15	26
Basal metab. rate	39	37	24
Sedimentation rate	28	2	70
Indican output	4	96	0
R. B. C.	35	30	35
W. B. C.	11	26	63
Hemoglobin	91	2	7
Blood pressure	35	9	56
Weight	15	20	65

The maximum and minimum changes are also recorded:

Test	Maximum Increase	Maximum Decrease
Blood calcium	7- 11	13.7- 8.9
Blood sugar	85-105	140- 85
Basal metab. rate	-18-+2	-10--38
Sedimentation rate	20- 23	45- 18
Indican output	0-+5	
R. B. C.	3,500,000-4,700,000	5,400,000-4,100,000
W. B. C.	4,800- 8,000	10,400- 6,600
Hemoglobin	80- 95	80-60
Blood pressure	110- 145	200-155
Weight	157- 161	156-112

In no case was there roentgen-ray evidence that the joint changes characteristic of atrophic or hypertrophic arthritis had progressed while the patient was under treatment. This may be of no significance, but in view of the length of time of the treatment (average 16 months), the writer views the roentgen-ray findings with optimism. So far as he knows, however, no detailed serial study of this problem has ever been undertaken and he is endeavoring at the present time to gather further information on this point. The sedimentation rate remained stationary or decreased in almost every case, which may be taken as evidence of systemic improvement. There was also a fairly constant lowering of high blood pressure in line with the improvement in hypertensive cases mentioned earlier in this article. Especially noteworthy is the material increase in indican output. This raises the fascinating theory that one of the underlying causes of arthritis may be a disturbance of the sulphur metabolism, and the writer wishes to suggest the frequent examination of the urine for indican as a means of determining, at regular intervals, whether the arthritic patient is improving

or not. He is now using this method extensively, and it is singular to note that the amount of indican found in the urine apparently gives a fair clinical index of the report which the doctor will receive from the patient on examination.

ACTION IN THE BODY

Detailed pharmacological studies would be necessary before any exact explanation could be given for the physiological effect of ortho-iodoxybenzoic acid in the body. Arkin⁵ has demonstrated the germicidal properties of this compound in the presence of blood serum. Hektoen⁶ showed that when injected intravenously, it caused a nonspecific stimulation of antibody formation in animals. Smith² points out the close structural similarity of ortho-iodoxybenzoic acid to salicylic acid, and Pemberton⁷ has described its action as that of a "glorified salicylate." Tabern⁸ gives the following explanation of its beneficial action in arthritis:

1. "It has a definite bactericidal action in the blood stream, and perhaps in infected membranes as well.
2. "It has been shown experimentally that it stimulates leukocytosis and aids antibody formation.
3. "Ortho-iodoxybenzoic acid and its salts strikingly increase the permeability of membranes.
4. "It increases lymph flow by 400 per cent.
5. "Ortho-iodoxybenzoic acid has an intense and prompt analgesic effect.
6. "It decreases muscle spasm and reduces swelling."

While not wishing altogether to take exception to the above, the writer would hazard a theory that calcium ortho-iodoxybenzoate achieves its beneficial results through its stimulating action on the peripheral circulation. With this in mind, a group of patients was selected, comprising Buerger's disease, varicose leg ulcers, and ulceration of the leg from faulty circulation in acute anterior poliomyelitis. This group was used as a yardstick to measure any possible circulatory improvement. The results obtained with these patients were so striking that the writer wishes to advance the theory that it is by the same means (i.e., stimulation of peripheral circulation) that the arthritic patient is improved. It is his intention to publish, as soon as possible, more definite data on this phase. Even now, one can say that, subjectively at least, calcium ortho-iodoxybenzoate improves circulation in the affected joints.

CONCLUSIONS

1. The beneficial effect of calcium ortho-iodoxybenzoate in a general group of 236 arthritic cases has been studied over a period of two years.
2. A more detailed study of 46 cases of hypertrophic and atrophic arthritis is also presented.
3. The therapeutic results were most satisfactory, and unpleasant side reactions were almost non-existent.

4. Laboratory findings indicate increase in indican output, improvement in hypertension and lowering of sedimentation rate.

5. A theory is advanced as to the physiological action of the drug in improving peripheral circulation.

BIBLIOGRAPHY

1. YOUNG, A. G., and YOUNG, J. B.: Use of o-iodoxybenzoic acid in treatment of infectious arthritis, *Jr. Am. Med. Assoc.*, 1926, lxxxvii, 746-752.
2. SMITH, M.: Use and action of o-iodoxybenzoic acid in treatment of arthritis, *Boston Med. and Surg. Jr.*, 1927, cxvii, 305-310.
3. COTTRELL, J. E.: Treatment of arthritis with salts of o-iodoxybenzoic acid, *Am. Jr. Med. Sci.*, 1927, clxxiv, 623-633.
4. WHEELDON, T. F., and MAIN, R. J.: Use of colloidal sulphur in treatment of arthritis, *Jr. Bone and Joint Surg.*, 1933, xv, 94-97.
5. ARKIN, A.: On the antiseptic and bactericidal action of the sodium salts of iodbenzoic, iodosobenzoic and iodoxybenzoic acids, *Jr. Pharmacol. and Exper. Therap.*, 1911, iii, 145-154.
6. HEKTOEN, L.: The influence of sodium iodoxybenzoate on the production of antibodies in dogs, *Trans. Chicago Path. Soc.*, 1909-1911, viii, 138-141.
7. PEMBERTON, R.: Arthritis and rheumatoid conditions, 1929, Lea and Febiger, Philadelphia, p. 283.
8. TABERN, D. L.: Arthritis and amiodoxyl benzoate, *Clin. Med. and Surg.*, 1928, xxxv, 741-744.

DR. RICHARD SHUCKBURGH AND YANKEE DOODLE *

By LOUIS H. RODDIS, F.A.C.P., Comdr. Medical Corps, U. S. Navy,
Washington, D. C.

OUR national airs and patriotic songs, like the weather, have always been considered the legitimate subject of criticism. The words are unsuitable, the music is not good, it is beyond the range of the average voice, or some other objection is advanced. No other patriotic song has come under fire more often than has the old fashioned tune and words of the Revolutionary War song, Yankee Doodle. The words are mere nonsense, say the critics, and the music is ridiculous, a mere hurdy-gurdy style of composition. Yet like many things that are nonsense—Mother Goose rhymes, for instance—it remains a popular favorite among our patriotic airs. It is the oldest of our songs of this class and has been sung for over 175 years. A song that has done this cannot be entirely devoid of merit and, furthermore, there is no evidence that its popularity is declining. The piece is really a very spirited little march of a truly martial character, and anyone who has swung along in a military formation to its bright staccato strain cannot but feel the reason for the regard in which it is held. As it was expressed as long ago as 1826:

Yankee Doodle is the tune
Americans delight in;
'Twill do to whistle, sing or play,
And just the thing for fighting.

There is a long standing controversy as to who was the author of Yankee Doodle, what were the original verses, and what was the origin of the tune. Without going into the details of this controversy, it would appear that the preponderance of evidence indicates that it was written in 1758 by a medical man, Dr. Richard Shuckburgh, a surgeon in the British Army. The music is believed to be an old jig tune well known in the eighteenth century. As originally written, it was probably intended as a good humored satire on the colonial militia who were employed in the French and Indian War and whose clumsy drill and somewhat miscellaneous attire contrasted in a marked degree with the precise manual of arms and scarlet array of the British regular troops.

In the Farmer and Moore Collections for 1824, under the title of

* Received for publication January 16, 1934.

This is the sixth of a series of portraits of medical poets. Those which have previously appeared in the ANNALS OF INTERNAL MEDICINE are:

Joseph Rodman Drake—February 1929
Oliver Wendell Holmes—June 1930
Oliver Goldsmith—May 1932
Wm. Savage Pitts—January 1933
Lieutenant Colonel John McCrae—June 1933

"Origin of Yankee Doodle" it was stated that in 1755, Dr. Shuckburgh (sic), a physician attached to the staff of General Abercrombie's army then encamped a little south of Albany, "to please Brother Jonathan composed a tune" and palmed it off on the colonial militia as a celebrated military march. The tune immediately became a favorite with the provincials. After realizing that a joke had been played upon them they enjoyed both the air and the joke, and later with a certain malicious touch they made it the popular air of the American Revolution.

Biographical facts regarding Dr. Shuckburgh are few in number. He was born in 1705. The name has led to his being described as of German extraction, but as a matter of fact he was born in the heart of England, in Shakespeare's own county of Warwick, and there is a hamlet of the name in the adjoining county of Northamptonshire. It is more than likely that he was descended from another Richard Shuckburgh, a member of the lesser gentry of Warwickshire, whose meeting with Charles I near the battlefield of Edgehill furnished the subject of a picture reproduced in Howitt's "Visits to Remarkable Places." The British army lists of the day show a Richard Shuckburgh as holding a commission dating from June 25, 1757, as surgeon in the "Four Independent Companies of Foot at New York." Shuckburgh was much interested in the Indians and in July 1759, Sir William Johnson, then the Royal Commissioner for Indian Affairs, appointed him as his secretary. Sir William mentioned in a letter of March 24, 1760, among his many qualifications for the post the fact that he had recorded all his (Sir William's) proceedings with the several nations of Indians since the opening of the last campaign. He appointed him to succeed a Captain Wraxall who had died the preceding year, but did not report his action to London in sufficient time to forestall another office seeker and a Mr. Marsh had already been selected for the post. Shuckburgh was thus "elbowed out," as he very graphically expressed it; but worse than that, as the King's Regulations did not permit him to hold two public offices at the same time, he had resigned his commission as surgeon of the Four Independent Companies and so found himself without either position. He did not get one until January 10, 1763, when he wrote Sir William as follows:

"I have completed my Purchase with the Surgeon of the Seventeenth Regiment and received my Commission from the General the 29th ult."

In 1765, he was stationed at Detroit but at the end of the year he returned to New York. Sir William Johnson who was Shuckburgh's patron and friend was an outstanding figure in colonial America. He was one of the first of our numerous "captains of industry" and "empire builders." He began as manager of estates in the Mohawk Valley belonging to his uncle, Sir Peter Warren, but bought land on his own account, building up an organization in real estate and fur trading almost as huge as some of our modern industries. Indeed, the Indians called him "Chief Big Business." He was the richest man in the colonies and as Indian agent for the British Crown exercised great influence over the destinies of the new land. The

warlike Iroquois acknowledged him as an honorary chief. He ruled the Mohawk Valley as an absolute monarch, with Johnson Hall near Albany as his palace. In every way he was a picturesque and interesting figure. He had numerous wives, mostly from the Indian tribes. He bought the first one, and later ones he did not have to buy. It was said he was the father of one hundred children, probably no exaggeration. He showed the greatest generosity and affection for them and provided lavishly for both wives and children. So colorful and influential a patron was not likely to be turned aside from any purpose and, Mr. Marsh having died, Shuckburgh was again recommended as Secretary of Indian Affairs, though he was not confirmed in his appointment until 1767. He did not surrender his commission this time until the appointment was secure. Dr. Thomas White did not succeed him as Surgeon of the Seventeenth Regiment until May 9, 1768.



FIG. 1. The Van Rensselaer house near Albany, New York, close to site of old Fort Crailo. Here Dr. Shuckburgh is believed to have written "Yankee Doodle."

He did not long enjoy his appointment due to failing health. On December 26, 1771, Johnson in a letter to the Earl of Dartmouth speaks of Shuckburgh as "aged and of late very infirm." On August 26, 1773, the *New York Gazette* printed his obituary notice as follows:

"Died at Schenectady, last Monday, Dr. Richard Shuckburgh, a gentleman of very genteel family, and of infinite jest and humour."

He had at least two children. A notice in an Albany paper mentions the christening of a son, John, by Richard and Mary Shuckburgh on March 15, 1747. Furthermore, he mentions in his later years, in one of his letters, his satisfaction at seeing his daughter well married (to a British officer).

Of the numerous theories regarding the origin of Yankee Doodle, it suffices to say here that the most probable one is that Dr. Shuckburgh wrote some verses to an old fashioned jig tune known by various names, but most commonly called Kitty Fisher's jig, and recommended them in jest to the provincials encamped with the regulars at old Fort Crailo. The tune, to use our present song writer phrase, "caught on" and there is no doubt but that it became a very popular air throughout New England and the colonies generally.

In the *New York Journal*, October 13, 1768, there is a mention of a celebration in which the bands used the "Yankee Doodle Song" as a principal piece. James Thacher in his "Military Journal" speaks of British troops marching out in 1775 to take part in the battle of Lexington, their band playing *by way of contempt*, Yankee Doodle. The adoption of the tune as a patriotic air gave it quite another aspect, however, a charge expressed by a British officer. Thomas Aubrey says in 1777, alluding to Burgoyne's surrender: "The soldiers at Boston used it as a term of reproach but after the battle of Bunker Hill, the Americans gloried in it. Yankee Doodle is now their poem, a favorite of favorites, played in their army, esteemed as warlike as the Grenadier's March. . . . After our rapid successes we held the Yankees in great contempt, and it was not a little mortifying to hear them play this tune, when their army marched down to our surrender."

What Dr. Shuckburgh's original verses were is not now positively known. The present ones are probably of Revolutionary War origin. Dr. George H. Moore, whose research on the subject was considerable, gives the following as having been part of the Shuckburgh verses:

There is a man in our town
I pity his condition.
He sold his oxen and his sheep
To buy him a commission.

These better known verses probably appeared during the first year of the American Revolution:

Father and I went down to camp,
Along with Captain Goodwin.
And there we saw the men and boys
As thick as hasty pudding.

Yankee Doodle keep it up,
Yankee Doodle Dandy.

When his commission he had got,
He proved a nation coward.
He durst not go to Cape Breton
For fear he'd be devoured.

Yankee Doodle came to town,
Put on his striped trousers,
And vowed he couldn't see the place
There was so many houses.

The place where Shuckburgh wrote the song is better authenticated. A granddaughter of General Robert Van Rensselaer, in a letter on the subject, says:

"The story of Yankee Doodle is an authentic tradition in my family. My grandfather, Brig. Gen. Robert Van Rensselaer, born in the Green Bush Manor House, was a boy of 17 at the time when Dr. Shuckburgh, the writer of the verses, and Gen. Abercrombie were guests of his father, Col. Johannes Van Rensselaer, in June 1758. We have a picture of the old well, with the high stone curb and well sweep which has always been associated with the lines written while the British surgeon sat upon the curb."

It is known that Abercrombie was at or near Albany in the spring of 1758, preparing for the attack on Ticonderoga, and it is very likely that Dr. Shuckburgh was with him. The house, a picture of which is reproduced here, is an old brick Georgian Mansion, long known locally as Old Fort Crailo, a name received apparently from its having been built on the site of a wooden stockade erected by the settlers in 1642 as a refuge during Indian raids. It was in 1924 made a State Monument and the house is being restored and used as a museum of Revolutionary relics and materials relating to Yankee Doodle and to the medical military poet who rendered it famous. No known portrait of Shuckburgh has been brought to light, although a considerable search has been made for one.

BIBLIOGRAPHY

1. Report by Library of Congress on the Star Spangled Banner and other patriotic songs, 1909, O. G. T. Sonneck.
2. National Music of America, 1900, L. C. Elson.
3. Field book of the American Revolution, 1860, B. J. Lossing.

EDITORIAL

WILLIAM HENRY WELCH

THE death of Dr. Welch has removed from the constantly changing medical scene one to whom the historian of the last half century of American medicine must ascribe a leading rôle in the development of medical science, medical education, and public health. The promotion of these advances was indeed the main theme consistently held to through his unusually long and active life, and his accomplishments in these fields outrank in significance his numerous and important personal contributions to the subjects of Pathology, Hygiene and the History of Medicine, in each of which he successively held the professorship in The Johns Hopkins Medical School.

In his youthful days in medicine, Welch had the most intimate personal experiences with the men and the environment that constituted American medical science and medical education in that period and likewise with those who were in the forefront of European medicine of that day.

He graduated from the College of Physicians and Surgeons, Columbia, in 1875, at a time when the medical course was almost entirely didactic, when the only laboratory course was that in anatomy and when the lectures and demonstrations in physiology, pathology and materia medica were given by clinicians who took a secondary interest in these fields of science. They lectured about the achievements of others, but neither in training nor in equipment were they fitted to contribute to the advance of knowledge. Very few of the medical schools in the United States had more than a perfunctory connection with a university, and even fewer owned and controlled a hospital. Welch himself took part in this educational system as head of a "quizz" and learned from personal experience also the difficulty of combining an active interest in pathology with the practice of medicine.

From his two periods of study in Germany and Austria and his visits to medical centers in France and England, Welch derived a clear and vivid understanding of the great advantages possessed by the system of medical research and education which had developed in European countries. It was a period in which tremendous advances in knowledge were being made and one also in which the importance of science was receiving practical recognition from universities and states in the form of special laboratories and equipment which enabled the masters in each field to devote all their time to their subjects and to gather about them assistants and students to aid in carrying forward their work. It was a golden age for the workers in these laboratories linked in a close camaraderie of enthusiasm and gathering with new tools and methods a rich harvest from relatively virgin fields.

Welch first went abroad for study in 1876. He had already while an intern in Bellevue Hospital under Delafield developed an interest in pathology

through the performance of a considerable number of autopsies and it was natural that he should desire to round out this experience by a period of study under Virchow, the master of cellular pathology. To acquaint himself first with histology, he worked for a semester under Waldeyer at Strassburg. There also he took a course under Hoppe-Seyler and Baumann in what was then the only existing laboratory for research in physiological chemistry. Later Welch was accepted as a student by Ludwig, whose laboratory or institute of physiology in Leipzig was in those days the most important center of research in this subject. It was Ludwig who at the end of the semester advised Welch to continue his pathological studies under Cohnheim at Breslau, rather than in Virchow's institute. Cohnheim was the coming master of general or functional pathology. In his laboratory were Weigert, Ehrlich, Albert Neisser, Salomonsen and others marked for brilliant future careers. Welch witnessed there the historic incident of Koch's demonstration of the anthrax bacillus. His own problem was the pathogenesis of pulmonary edema, and he carried out a clear and logical series of experiments which led to his publication of his theory of the causative influence of disproportionate action of the two ventricles.

The eight months with Cohnheim were the high point of Welch's first two years abroad, though after this he worked with Chiari in Vienna and von Recklinghausen in Strassburg and visited in Paris and London before returning to New York in 1878.

From this first journey he came home not only abreast of his day in knowledge of pathology and the technic of pathologic research but with a clear conception of the necessity of an adequate laboratory and of students to progress in this field of science. He had come home with a program. The first step to its fulfillment was made possible by an offer from Bellevue Medical College of three rooms for a laboratory of pathology, the first of its kind in this country. Six lean years followed, in which to earn a necessary living he devoted part of his time to running a student "quizz" and part also to clinical practice. It was a test of his fidelity to science, and that he triumphed is shown by the success of his department of pathology and the number of students from various schools who came to attend his courses.

At the end of that time he was invited to become Professor of Pathology in The Johns Hopkins University and pathologist to The Johns Hopkins Hospital. The medical school had not yet been organized and the Hospital was still in the process of construction, but the University had already made a name as a home for science, and Welch did not hesitate to accept the opportunity.

Before moving to Baltimore, however, he spent another year abroad which was to prove even more significant to his future than his first visit there. This time he went to acquaint himself with the rapidly developing science of bacteriology. In that crowded year he learned technic from Frobenius, studied hygiene in von Pettenkofer's institute and under Flügge,

animal pathology under Kitt, and finally bacteriological methods under Koch himself. It was a "golden decade" in the history of medicine, a decade which saw the discovery of the tubercle bacillus, the bacillus of typhoid fever, the causative agents of pneumonia and of Asiatic cholera. "Those who did not live through that period," said Welch in later years, "can hardly realize the thrill and enthusiasm attending the unlocking of the great secrets of the causation and spread of that most important group of human diseases, the infectious diseases." The close contact he enjoyed with the great figures of those days not only stimulated his own productiveness in the field of bacteriology but awoke early his realization of the great importance of preventive medicine and hygiene.—He had added another feature to his program.

Within a matter of months it will be fifty years since Welch came to The Johns Hopkins University and the man and the opportunity were joined. In that time American medical science, medical education and public health have experienced a development which in its rapidity and extent is unparalleled. We have attained a parity and in certain respects have surpassed the attainments of those European nations which a half century ago were so immeasurably our superiors in these fields. The full history of these crowded years remains to be written. Many forces contributed to produce this result, but it is certain that no other man exerted such a guiding influence upon the course of events as William Welch.

In attempting now at the completion of his career to assay the significance of its different phases, we come to feel that the chief value of his active years as Professor of Pathology and as first Dean of the Medical School of The Johns Hopkins University lay in the demonstration furnished by his department and the whole school of the results that might be expected from a university type of medical education.

Welch had played a large rôle in the selection of the clinical faculty and later of the heads of the departments of preclinical sciences. The roll of names, Osler, Halsted, Kelly, Abel, Mall, and Howell, testify to the wisdom shown in their selection. The plan of organization of the Medical School which was adopted was drawn up by Welch. It created a sensation in the medical circles of those days, and it is a measure of the distance we have come that today it would be accepted as a matter of course.

That the Hospital should be a part of the Medical School was provided in the will of its founder, and that the Medical School should be an integral part of the University had also been decided. It was considered revolutionary, however, that the requirements for admission to the Medical School should include a collegiate degree with required work in fundamental science and a reading knowledge of French and German. "At present," said Welch in an address in 1893, "no medical school requires for admission knowledge approaching that necessary for entrance into the freshman class of a respectable college; many schools demand only the most elementary education, and some require no evidence of any preliminary education

whatever." The medical course in the new school was to occupy four full years. The amount of didactic teaching was to be minimal and the larger amount of time was to be spent in practical work in the laboratories and in the wards of the hospital. The occupants of the chairs of anatomy, pharmacology and physiology were to devote all their time to teaching and research, and research was recognized as an essential aid in teaching. In the enunciation of almost every one of these principles new ground was broken.

It remained to justify by works the soundness of these principles and this was done in full measure. Within a few years the success of the new school was assured by the constant output of its important scientific and clinical publications, the enthusiasm of its undergraduate and graduate students and by the tendency evident throughout the better schools to adopt many of the features of its program. Welch's share in this success was a very large one. These were the years of his most active work in pathologic investigation and as a teacher of pathology. His studies of thrombosis and embolism, hog cholera, the etiology of pneumonia, his identification with Nuttall of the gas forming bacillus (*B. welchii*) may be selected from over 300 titles for special mention. But the output of trained pathologists from Welch's laboratory was even more important, for many of these men were destined to carry not only his instruction in pathology but his educational ideals into a large number of the medical schools of the country. The list of professors of pathology who had been students of Welch is too long for citation. In 1914 there were 113 graduates of The Johns Hopkins Medical School who held professorial chairs throughout the country and many hundreds more, of course, engaged in teaching. Before the foundation of The Johns Hopkins, other schools, notably Harvard under President Eliot and the University of Michigan under Angell, had achieved significant advances in standards, but it had remained for The Johns Hopkins under the guidance of Welch, unhampered by tradition, to overwhelmingly demonstrate the success of a university type of medical school and through the influence of its graduates to play the major rôle in stimulating a general elevation in standards.

In the accomplishment of this beneficent revolution, many factors played a part. It would have been impossible without the establishment within this period of the great philanthropic foundations and the stimulation to large individual gifts for construction and endowment. The action of the medical profession itself through the American Medical Association in establishing standards and grading existing schools in accordance with these standards, and finally the raising of educational prerequisites by the state licensing boards, were all essential steps in the great advance.

It was natural, however, with so much activity in this field that the opinion of Welch should have been frequently sought. Those who thus came to Baltimore were impressed not only with the breadth of his knowledge but equally with his insight into practical difficulties. His influence

grew also because there was no bitterness in his spirit and no fanaticism in his advocacy of new methods. He deplored the utterances and actions of some of his disciples who could see no good in the past and who stirred up conflict by their slurs upon the motives of all who opposed them. There was a breadth and equanimity to Welch's personality which set him apart.

Such calls for advice became so numerous and insistent that he was gradually forced out of active work in pathology and into the position of unofficial consultant to innumerable enterprises whose aim was the betterment of medical education. It is probably this phase of Welch's career which contains his greatest contribution, but so modestly and so quietly did he carry his share in the labors of those days that the history of his influence upon events is as yet largely unwritten. Few institutes or departments for medical research were founded in the early part of this century without Welch having contributed from his wide experience either to their form of organization or to their selection of personnel. The policies formulated by the trustees of great endowments to apply to the betterment of humanity have in a large number of instances derived their inspiration, if not their actual wording from counsel that was sought and obtained from Welch.

His relations to the General Educational Board and to the Rockefeller Foundation were exceedingly close. He was the President of the Board of Scientific Directors. His wide knowledge of the various fields of medical science; his extensive personal acquaintance with men and with their work and his flair for practical affairs enabled him to exert great influence in determining the direction of the efforts and the recipients of the benefactions of this great foundation. Thus it came about that in time he played a part vicariously in health surveys and campaigns for health in many foreign lands and that he had the satisfaction of seeing American aid extended to institutions for medical research and education in some of those European countries to which he had gone as a student.

One of the important features of the change in medical education upon which Welch had laid great stress was the full time principles as applied to the preclinical sciences. That the development of science in this country was greatly advanced by the widespread adoption of this part of Welch's program there can be no doubt. Its success led him and many others to consider the application of the same rule to the heads of the clinical departments, and since 1914 a number of schools including The Johns Hopkins Medical School have instituted full time chairs of medicine, surgery, and of some of the other leading clinical departments. The success of this new departure has perhaps not been as striking as that which attended the earlier improvements in the organization of medical schools, but that in some modified form it will persist seems evident.

Welch had from the first a deep interest in the broader aspects of public health and preventive medicine. He gave very freely of his time to many of the great movements in this field which originated at the beginning of this century. In Baltimore he took an active part in local health problems

and as President of the State Board of Health he acquired practical experience with the details of health administration and with the formulation of state laws dealing with health problems. He served as Chairman of the first International Congress of Tuberculosis held in this country in 1908, and was a frequent visitor to such congresses abroad. Welch considered that the greatest coming medical advances were to be in the field of prevention. This aspect of his interests eventually led to the formation of the School of Hygiene and Public Health at The Johns Hopkins University, which was organized according to a broad program outlined by Welch and for which he selected the personnel. He himself was its first head and saw it through the first years of its existence. Its influence on the standards of public health education in this country and on research in problems of hygiene and public health may in time equal that exerted earlier in other fields by the school of medicine.

Welch withdrew from the direction of the School of Hygiene, but it was not in order to retire. At the age of seventy-six he turned his unquenchable energy into the accomplishment of an earlier dream, the foundation of a Department of the History of Medicine. It is housed today in a noble building, the William H. Welch Library. He spent several happy years collecting personally in the bookshops of Europe some of the treasures now on the library shelves, and then as the shadows of his final illness began to gather he turned over the direction of the Department to an able successor, Professor Sigerist.

Few men have been more honored in their life time than Welch, perhaps in part because he himself never sought prominence and public honors; and was known for the unselfishness of his interests. He was devoted not only to his ideals of science and education but also to the welfare of those men who were advancing these ideals. Many men of prominence in medicine owe their first step from obscurity to the helping hand of Welch. It came about quite naturally that the plan for an international celebration of his eightieth birthday should have been taken up with enthusiasm throughout the medical world. Its focal point was the great gathering in Memorial Continental Hall in Washington where a distinguished audience, including the President of the United States as one of the speakers, rendered homage to the accomplishments and the personality of this great American man of Science.

Virchow, whose career is in some ways similar to that of Welch, once wrote: "There are also those who if they do not create the current, still give to it its direction and force. These men are not always the happiest. Many go down in the movement, or by it. Many grow weary after they have given to it their best forces. Much power and great tenacity are necessary if the individual shall not only live to see his triumph but also to enjoy it." That necessary power and tenacity were preëminent in Welch. His addresses in the period of the opening of The Johns Hopkins Medical

School contain his program of medical education; it will be found again unchanged by those who read his address at the opening of the Medical School of the Duke University, forty years later. This program was an adaptation of the educational methods he had found in Europe. Welch diverted this current of progress into American channels and gave it its force. His fairness, his wisdom founded on his historical perspective and knowledge of men, and his lack of selfish ambition spared him the bitterness of personal opposition, so that he lived still unwearied to see his triumph and also to enjoy it.

REVIEWS

Human Sex Anatomy. By ROBERT LATOU DICKINSON, M.D., F.A.C.S. viii + 145 pages; 24 × 30 cm. The Williams and Wilkins Company, Baltimore. 1933. Price, \$10.00.

As is implied by the title, the chief function of this book is to serve as a topographical atlas for those who are interested in the study of the generative organs of the two sexes. However, the first 150 pages of this volume are given over to text in which the author frankly discusses human sexual relations from the point of view of physiology as well as that of anatomy.

Dr. Dickinson emphasizes the fact that there is an art of sexual intercourse, a fact most men do not appreciate. He points out that it is just as important for marital happiness that the woman obtain full sexual gratification from coitus as it is for the husband. The author offers suggestions that may prove helpful in bringing about this end. Physicians are apt to examine women complaining of sexual difficulties for such gross anatomical defects of the genitalia as imperforate hymen and absence of the vagina, but often they do not realize the part that minor variations in the size of the genitalia of the two sexes may play in sexual incompatibility. Gynecologists and the medical profession as a whole will find the discussion in the first part of this book of help in treating women complaining of dyspareunia and of lack of sexual feeling.

The drawings that make up the larger part of the volume are based on numerous carefully taken measurements of the various parts of the genitalia of the two sexes. Because these measurements were taken on living subjects rather than from cadavers, this atlas is of special value. Great pains have been taken to make the illustrations accurate.

As has already been said, at least a few of the many facts brought out by the author will doubtless prove of value to the clinical gynecologist. However, the main use for this very complete atlas will probably be as a reference book which anatomists and physiologists studying problems of the generative tract may consult with profit.

L. B.

Heredity and Environment; Studies in the Genesis of Psychological Characteristics.

By GLADYS C. SCHWESINGER and FREDERICK OSBORN, American Museum of Natural History. 484 pages. The Macmillan Company, New York. 1933. Price, \$4.00.

This book, written by experienced clinical psychologists, is not intended for light reading, but as a reference work it is of great value. As the authors state: "This volume was prepared as part of an attempt to appraise the present status of knowledge in the field of eugenic research."

No attempt is made to persuade the reader to become a convert to either the thesis of heredity or environment. But arguments from both schools are presented fully, and copious references are given. In the six chapters and appendix the topics of Measurement of Intelligence, Measurement of Personality, Definition of the Heredity and Environment Problem, A Study on Genetic Factors and Stated Environmental Differences as They Affect the Development of Intelligence, and Viewpoints of Personality are discussed.

The final conclusions set down by the authors are well taken: "The extreme conclusions frequently voiced by some 'Environmentalists' on the one hand or by the extreme 'Hereditarians' on the other, do not find justification in the facts. They exceed the limits set by the studies already available which no thoughtful student can

longer afford to ignore: The evidence that there are important differences among individuals in heredity capacity for intelligence, is entirely conclusive; the variabilities and averages of large numbers of individuals under influences of varying environments are in process of being quite accurately determined."

J. L. McC.

Phyloanalysis: A Study in the Group of Phyletic Method of Behavior-Analysis. By WILLIAM GALT, M.A.; with a preface by TRIGANT BURROW, M.D. 151 pages. Baker and Taylor Co., New York. 1933. Price, \$1.00.

This small book presents a very interesting discussion of certain aspects of experiments in organic psychiatry as based on observations that have to do with the physiological reactions of man as they are expressed subjectively or in the sphere of his own feelings. The author claims that "the place occupied by this field of investigation in respect to man's behavior-disorders is analogous to the place occupied by bacteriology in relation to structural medicine"; and he further states that "phyloanalytic technic does not represent so much an effort to prove the existence of something as to note the existence of impediments."

J. L. McC.

COLLEGE NEWS NOTES

GIFTS ACKNOWLEDGED

Acknowledgment is made of the following donations by members to the Library of the College by the authors:

Dr. Howard F. Root (Fellow), Boston, Mass.—1 monograph, "The Association of Diabetes and Tuberculosis";

Dr. Myrton S. Chambers (Fellow), Flint, Mich.—1 reprint;

Dr. Arthur H. Jackson (Associate), Washington, Conn.—1 reprint;

Dr. Alfred J. Scott, Jr. (Fellow), Los Angeles, Calif.—2 reprints.

NEW LIFE MEMBER

Dr. James Murray Washburn, Chicago, Ill., became a Life Member of the College on April 20, 1934.

Sir Aldo Castellani (Fellow), Director of the Ross Institute of Tropical Hygiene, London School of Hygiene and Tropical Medicine, has returned to New Orleans to begin his duties as Professor of Tropical Medicine at the Louisiana State University Medical Center. Dr. Castellani will spend a part of each year at the University.

Dr. Lawrence Kolb (Fellow), U. S. Public Health Service, is in charge of the new U. S. Hospital for Defective Delinquents at Springfield, Mo. The hospital will be used only for prisoners over whom the Federal Government has assumed jurisdiction. It is considered an essential unit in the government's attempt to specialize the treatment of persons committed to its care. It will serve as the medical center for the entire federal penal system. The center will accommodate 705 patients; it is located on a site consisting of 445 acres donated by citizens of Springfield, Mo.; it consists of eight buildings, erected at a total cost of over two million dollars.

An informal social luncheon of the Fellows of the American College of Physicians residing in North Carolina was held at Pinehurst on May 2, 1934, with Dr. Charles H. Cocke, Governor of the College for North Carolina, presiding. Twenty-four Fellows were present, including the following Officers of the North Carolina State Medical Society:

Dr. Isaac H. Manning, Chapel Hill, outgoing President;

Dr. P. P. McCain, Sanatorium, the newly installed President;

Dr. Paul H. Ringer, Asheville, President-Elect;

Dr. Robert L. Felts, Durham, First Vice-President; and

Dr. L. B. McBrayer, Southern Pines, Secretary-Treasurer.

At the 37th annual meeting of the American Gastro-Enterological Association at Atlantic City, May 1, Dr. B. B. Vincent Lyon (Fellow), Philadelphia, was elected President. Dr. Chester M. Jones (Fellow), Boston, was elected Second Vice-President, and Dr. Russell S. Bales (Fellow), Philadelphia, was reelected Secretary.

Dr. Howard F. Root (Fellow), Boston, Mass., addressed the Scranton County Medical Society, Scranton, Pa., on "Practical Problems in Diabetes" on May 1. He also gave a two-hour clinic at the Scranton State Hospital on "Dietary Treatment in Diabetes" the same day.

Dr. Robert A. Peers (Fellow), Colfax, Calif., was unanimously chosen President-Elect of the California Medical Association at its recent annual meeting held in Riverside.

Dr. Oliver T. Osborne (Fellow), New Haven, Conn., is the author of an editorial entitled "Clinical Histories" published in the *Medical Record* of May 16, 1934.

Dr. Herbert L. Bryans (Fellow), Pensacola, Fla., was chosen President-Elect of the Florida Medical Association at its 61st annual meeting held in Jacksonville, April 30 to May 2, 1934.

Dr. Bryans is also President of the Florida Heart Association, and Vice-President of the Emory Medical Alumni Association of Florida.

Dr. Walter L. Bierring (Fellow), Des Moines, Iowa, delivered the oration in medicine, entitled "Diagnosis of Heart Disease: Historical Development of Its Recognition," before the Illinois State Medical Society's 84th annual meeting at Springfield, May 15 to 17.

The American Academy of Tropical Medicine was organized in Washington during February, under the auspices of the National Research Council. Dr. Charles F. Craig (Fellow), New Orleans, was elected Vice-President, and Dr. Earl B. McKinley (Fellow), Washington, was elected Secretary. The aim of the Academy is "to stimulate interest in all phases of tropical medicine, to provide current surveys of work in progress, to coördinate American work to prevent duplication, to function as a central source of information for investigators, to coöperate with other agencies in the same field and to receive and administer funds through grants for specific projects."

Honorary degrees were conferred at the centennial celebration of Ohio State University College of Medicine, at Columbus, March 1 to 3, on Dr. Torald H. Sollmann (Fellow), Dean, Western Reserve University School of Medicine, Cleveland; Dr. William S. McCann (Fellow), Director of the Department of Medicine, University of Rochester School of Medicine, Rochester, N. Y.; and Dr. Henry S. Houghton (Fellow), Director of the University Clinics, University of Chicago.

Dr. Joseph F. Bredeck (Fellow), St. Louis, Mo., gave one of the evening addresses in connection with the Graduate Course and Clinic Conference held in St. Louis, May 21 to 26, under the auspices of the St. Louis Clinics.

Dr. Walter C. Alvarez (Fellow), Rochester, Minn., was a guest speaker at the 153d annual meeting of the New Hampshire Medical Society, held in Manchester, May 15 to 16.

Dr. Jonathan C. Meakins (Fellow), and Dr. James B. Collip (Fellow), both of Montreal, were guest speakers on the occasion of the 7th annual "Postgraduate Day" of the Mahoning County Medical Society, Youngstown, Ohio, on April 28.

Dr. W. McKim Marriott (Fellow), St. Louis, Mo., was the guest speaker on the occasion of the annual meeting of the Oklahoma Pediatric Society on May 21 at Tulsa.

Dr. Judson Daland (Fellow), President of the Philadelphia Institute for Medical Research, discussed plans of the Institute and its organization at a special meeting of the Philadelphia County Medical Society, April 30.

Dr. Leonard G. Rowntree (Fellow), Director of the Institute, spoke on "The Accruing Effects of Thymus Extract (Hanson) on Growth and Development in Successive Generations of Rats."

Dr. E. B. Krumbhaar (Fellow), Dr. Leonard G. Rowntree (Fellow), Dr. William D. Stroud (Fellow), and Dr. James B. Wolffe (Associate), were among those who gave demonstrations of methods of diagnosing and treating heart disease under the auspices of the Philadelphia Heart Association, May 15 to 18.

At the 53d annual session of the South Dakota State Medical Association at Mitchell, May 14 to 16, the following were among the visiting physicians addressing the meeting:

Dr. Francis E. Senear (Fellow), Chicago, "Modern Treatment of Syphilis";

Dr. Fred M. Smith (Fellow), Iowa City, "Peptic Ulcer";

Dr. Albert M. Snell (Fellow), Rochester, Minn., "Unusual Clinical Pictures Associated with Common Duct Stone";

Dr. Frederick A. Willius (Fellow), Rochester, Minn., "Treatment of Congestive Heart Failure."

Dr. Lea A. Riely (Fellow), Oklahoma City, Okla., addressed the 68th annual session of the State Medical Association of Texas at San Antonio, May 14 to 17, on the topic "Diabetic Problems."

Dr. David J. Davis (Fellow), Chicago, was elected Vice-President of the Society of Medical History of Chicago on May 2.

Dr. Frederick T. Lord (Fellow), Boston, Mass., has been elected President of the Massachusetts Tuberculosis League.

Dr. Alexander B. Moore (Fellow), Washington, D. C., will deliver the first of the Russell D. Carman Memorial Lectures in radiology at the meeting of the Minnesota State Medical Association at Duluth, July 16.

Dr. Charles H. Macey (Fellow), Pittsburgh, Pa., was a guest speaker at the annual meeting of the Virginia Tuberculosis Association at Richmond, April 5, his subject being "Tuberculosis in the Negro."

ABRIDGED MINUTES OF THE BOARD OF REGENTS

CHICAGO, ILLINOIS

April 15, 1934

The Board of Regents of the American College of Physicians met and was called to order at the Palmer House, Chicago, Ill., at 2:40 p.m., April 15, 1934, by the President, Dr. George Morris Piersol.

The following members of the Board of Regents were present: Dr. George Morris Piersol, Dr. Charles G. Jennings, Dr. Jonathan C. Meakins, Dr. William D. Stroud, Dr. William Gerry Morgan, Dr. James S. McLester, Dr. James Alex. Miller, Dr. Sydney R. Miller, Dr. David P. Barr, Dr. Arthur R. Elliott, Dr. James B. Herrick, Dr. Clement R. Jones, Dr. S. Marx White, Dr. Walter L. Bierring, Dr. John H. Musser, Dr. O. H. Perry Pepper, Dr. Francis M. Pottenger, Dr. Luther F. Warren, Dr. Maurice C. Pincoffs, and Mr. E. R. Loveland, Executive Secretary.

The Executive Secretary acted as Secretary of the meeting.

An abstract of the Minutes of the previous meeting of the Board of Regents, held at the College Headquarters, Philadelphia, Pa., December 3, 1933, was read and approved.

The Executive Secretary stated that he had received a communication from Dr. Noble Wiley Jones regretting his inability to attend because of the sudden illness of his father; also one from Dr. James H. Means stating that he would arrive on Thursday. With the permission of the Board, the presentation of other communications was deferred until later, due to the pressure of more important matters to be covered first.

President Piersol expressed his appreciation of the effort made by the Regents and Officers to come to the meeting a day previous to the opening of the regular Session. He also reported upon the preparation of the program of General Sessions.

Dr. James B. Herrick, General Chairman of the Eighteenth Annual Clinical Session, reported upon the work of himself and his committees. Dr. Arthur R. Elliott, Chairman of the Committee on Clinics, likewise presented the report of the work of his committee.

The Executive Secretary reported that the Ellis Research Laboratories of Chicago had applied for exhibit space and had made the usual deposit of \$10.00, but that the Committee on Exhibits had withheld their approval of the proposed exhibit of this firm. The Ellis Research Laboratories refused to accept this decision and filed suit, charging breach of contract. The Executive Secretary immediately employed the counsel that represents the American Medical Association. The court upheld the right of the College to refuse exhibits not acceptable to its Committee.

Upon motion by Dr. Herrick, seconded by Dr. Pottenger and unanimously carried, it was

RESOLVED, that the action of the Executive Secretary in the above matter be approved and the expenditure of such moneys as are necessary to satisfy the attorney's fee be authorized.

Preceding a report from the Committee on Specialization, Dr. Walter L. Bierring, who has attended various meetings of the Council on Education of the American Medical Association and other groups investigating a plan for the certification of specialists, reported that an organization was effected on February 11, 1934, known as the National Advisory Board for the Medical Specialties, comprising the four specialty boards now organized in ophthalmology, otolaryngology, obstetrics and gynecology, and dermatology. In addition, there is represented the National Board of Medical Examiners, the Federation of State Medical Boards and the Association of American Medical Colleges. In the selection of officers, the President, Dr. Louis B. Wilson, was taken from the Association of American Medical Colleges; the Vice President, Dr. J. S. Rodman, from the National Board of Medical Examiners; and the Secretary, Dr. Titus, from the Board of Obstetrics and Gynecology. On the Executive Committee, there was selected a representative from the Board of Otolaryngology, from the Board of Ophthalmology and from the Board of Dermatology. Their Constitution provides that no constituent member of the National Advisory Board shall be governed in its own organization by the action of this Board. The Board is purely an advisory one concerning itself with the determination of new specialty boards as to whether they are properly qualified and represent, in each instance, the national association in the particular specialty, and the section in the American Medical Association.

After these boards are organized and functioning, a register is to be maintained through the office of the American Medical Association in which certificate-holders will be recorded. The question of whether such organizations as the College of Surgeons and the College of Physicians should enter into this work was discussed, and it seemed the wisdom of most of those present that this new advisory board should concern itself entirely with the qualifications of specialists in the more strict sense. Dr. Bierring's impression from the meeting on February 11 was that an examining board in internal medicine, considering the broad field

that is covered by that subject, would be inadvisable, but that the separate Colleges might set up as one of their qualifications for admission a definite qualifying examination.

On the other hand, a board is to be established for the pediatricians, on which the American Academy of Pediatrics, the American Pediatric Association and the Section on Pediatrics of the American Medical Association will have representation. When such a body sets up a board, and that is considered a specialty, Internal Medicine might be considered also as a specialty. Dr. Bierring suggested that for the present, the American College of Physicians may be interested in this new movement, and possibly be prepared to give advice, if called for, but that it should not take an active part in the matter of the qualifications of specialists. He further expressed the opinion that the College should have some form of examination for admission, adopted after the plans of the older Colleges on the Continent.

Dr. James S. McLester also commented upon the manner in which the work of the National Advisory Board for the Medical Specialties would work. At the present time, the American Medical Association publishes in its Directory, opposite any man's name, the specialty that he claims. When the various examining boards begin to function, the American Medical Association presumably will take the results of these examinations for designation of specialties. The Council will be guided largely by the advice of the National Advisory Board as to the character of examinations and as to whether these certain examining boards are conducting the examinations in such a manner that their certificates can be accepted. The Council will be guided also by advice from other sources, if necessary, and they do not bind themselves always to accept the advice of any particular organization. The National Advisory Board will have as one of its chief functions the coördination of the work of the special societies.

Dr. McLester further pointed out that it is relatively easy to organize this sort of work for the otolaryngologists, ophthalmologists, gynecologists and obstetricians, but the work of organizing examinations for the surgeon and for the internist is a much more difficult matter, because of the greater breadth of the examination.

The report from the Committee on Specialization was postponed until the next meeting of the Board of Regents.

Dr. Sydney R. Miller, Chairman of the Committee on Credentials, presented candidates for Associateship and Fellowship, whose credentials had been carefully reviewed and whose election was recommended to the Board of Regents. (The complete list of elections, consisting of 96 Associates and 65 Fellows, was published in the May issue of the ANNALS OF INTERNAL MEDICINE.)

The report of the Committee on the John Phillips Memorial Prize was presented by its Chairman, Dr. David P. Barr, and was as follows:

"The Committee recommends that the Board of Regents authorize the preparation of a medal to be known as the 'John Phillips Memorial Award for Outstanding Achievement in Medicine,' this medal to be awarded at intervals on recommendation of the Committee and with the approval of the Board of Regents.

"Inasmuch as the annual expense after the initial preparation of the medal will not exceed \$200.00, the Committee ventures to suggest that the College extend its activities in two directions:

"(a) By establishing a Convocational lectureship, the lecturer to receive no honorarium but to have his expenses paid by the College.

"(b) By establishing a Fellowship in the amount of \$1800.00 to be known as the 'Research Fellowship of the American College of Physicians' and to be awarded each year on the recommendation of the Committee and the approval of the Board of Regents."

There was general discussion of the recommendations of the Committee by Dr. James Alex. Miller, who considered the recommendation as being in the line of progress, looking toward the stimulation of research rather than simply a cash recognition of something that had already been accomplished; by Dr. Jonathan C. Meakins, who referred to the original John Phillips Memorial Award as a recognition for medical research and expressing the opinion that the College would do well, if its financial condition permits, to foster research; by Dr. William D. Stroud, who stated that the income from the Endowment Fund is at present adequate to provide for the carrying out of the recommendations of the Committee.

On motion made by Dr. O. H. Perry Pepper, seconded by Dr. S. Marx White and regularly carried, the report of the Committee on the John Phillips Memorial Prize, including the recommendations, was adopted.

Secretary-General Morgan reported the following life membership subscriptions having been received during 1934:

Samuel E. Thompson, Kerrville, Tex.
 Philip H. Jones, New Orleans, La.
 Philip I. Nash, Brooklyn, N. Y.
 E. Moore Fisher, Washington, D. C.
 Frederick O. Fredrickson, Chicago, Ill.
 Jabez H. Elliott, Toronto, Ont.

The Secretary-General also reported the following deaths since the last meeting of the Board of Regents, December 31, 1933:

Fellows:

A. D. Dunn, Omaha, Nebr.	January 8, 1934
Adrian H. Grigg, Beckley, W. Va.	January 6, 1934
George T. Harding, Jr., Worthington, Ohio	January 18, 1934
Albert Hoff, North Bend, Nebr.	January 27, 1934
George G. Hunter, Los Angeles, Calif.	December 12, 1933
Frank Chambliss Johnson, New Brunswick, N. J.	January 1, 1934
Julian T. McClymonds, Berkeley, Calif.	December 4, 1933
George E. McKean, Detroit, Mich.	February 4, 1934
Paul E. McNabb, Manila, P. I.	February 24, 1934
Roger S. Morris, Cincinnati, Ohio	March 1, 1934

Associates:

Joseph Bringhurst, Felton, Del.	February 6, 1934
---------------------------------	------------------

Secretary-General Morgan further reported that a Committee was appointed at the last meeting of the Board of Regents to consider the advisability of having a suitable certificate prepared for our Life Members and, in the event that its preparation seems advisable, to suggest the type and wording of the certificate. The Committee recommended to the Board of Regents the adoption of a certificate and presented a suggested form which, after discussion by the Board of Regents, was directed to be revised and presented at the following meeting of the Board.

Secretary-General Morgan explained to the Regents an inadvertence on his part as signing as Secretary-General of the American College of Physicians a telegram to the House Judiciary Committee in connection with a bill on birth control.

Dr. Walter L. Bierring presented the following resolution, which was seconded by Dr. White and unanimously adopted:

RESOLVED, that it be recorded in the Minutes of this meeting that the explanation given by Dr. William Gerry Morgan of the incident concerning his signature as Secretary-General of the American College of Physicians to a telegram to the House Judiciary Committee in connection with one of the hearings on the birth control bill be accepted as entirely satisfactory, and that an expression of fullest confidence on the part of the Board of Regents in Dr. Morgan, in constantly guarding the interests of the College, be also recorded.

Adjournment.

ABRIDGED MINUTES OF THE BOARD OF REGENTS

CHICAGO, ILLINOIS

April 17, 1934

The second meeting of the Board of Regents of the American College of Physicians met and was called to order in the Palmer House, Chicago, Ill., April 17, 1934, at 12:45 o'clock, President Piersol presiding.

The following were present: Dr. George Morris Piersol, Dr. Charles G. Jennings, Dr. Jonathan C. Meakins, Dr. William D. Stroud, Dr. William Gerry Morgan, Dr. William J. Kerr, Dr. James Alex. Miller, Dr. Sydney R. Miller, Dr. David P. Barr, Dr. James B. Herrick, Dr. Clement R. Jones, Dr. S. Marx White, Dr. Walter L. Bierring, Dr. John H. Musser, Dr. O. H. Perry Pepper, Dr. Francis M. Pottenger, Dr. Luther F. Warren, Dr. Maurice C. Pincoffs, Dr. Ernest B. Bradley, Dr. Charles F. Martin, Chairman of the Finance Committee, and Mr. E. R. Loveland, Executive Secretary.

Upon motion made by Dr. Musser, seconded by Dr. Warren and carried, the reading of the Minutes of the last meeting was dispensed with.

Dr. James Alex. Miller presented the following report of the Committee on Specialization.

"The Committee on Specialization has carefully considered the suggestion that the American College of Physicians might establish a National Examination Board for the certification of specialists in internal medicine, similar to such boards already established for other special branches of medicine.

"It is the opinion of your Committee that at the present time the establishment of any such Board is neither feasible nor desirable. From its consideration of this question, however, your Committee has reached very definite conclusions looking forward toward more adequate and rigid requirements for admission to Fellowship and Associateship in the College.

"We beg leave to offer to the Board of Regents the following recommendations directed toward that end:

"(1) That in addition to the present requirements for Associateship those candidates who have been approved by the Committee on Credentials be required to pass a written examination in internal medicine.

"(2) That this examination be prepared by a special examining committee and that opportunity be offered for the examination to be taken at numerous convenient points throughout the country, the sealed papers to be returned to the examining committee who would then recommend the successful candidates to the Regents for election to Associateship.

"(3) That an examination fee of \$10.00 be required for taking this examination, which fee would be deducted from the regular initiation fee in the case of successful candidates upon their election to Associateship.

"(4) If the Board of Regents approves this examination plan in principle it is recommended that a new committee be appointed to work out the details of such a plan and report at the next meeting of the Board of Regents. Your Committee suggests that it would be proper and desirable to have the Committee on Credentials represented upon such a committee, and also that it would be desirable to have the personnel of the committee so composed that it would represent Fellows not connected with teaching institutions, as well as those who are so connected.

"(5) Your Committee further suggests that if such a proposed written examination plan be adopted, and is successful, that at some later date an additional clinical examination for candidates for Associateship might possibly be required, open to those who have passed the written test.

"(6) Your Committee also suggests that similarly at some later date it might be desirable to consider the requirement of an examination for promotion from Associateship to Fellowship.

"Your Committee wishes to express its obligation to Dr. Walter L. Bierring for his valuable counsel in the preparation of this report.

Respectfully submitted,

J. C. MEAKINS

J. H. MUSSER

J. A. MILLER, *Chairman.*"

Upon motion by Dr. White, seconded by Dr. Barr and regularly carried, it was

RESOLVED, that the above report of the Committee on Specialization be adopted.

President Piersol stated that his interpretation of the report is that the Board of Regents go on record as being in favor of this modification of our rules, in principle. The details of how this matter may be accomplished must be left to a committee to be appointed by the incoming President, this committee to consider the matter in detail and to report back to the Board of Regents at their next meeting.

Dr. James Alex. Miller suggested that it may be possible that the committee, after going into the details more thoroughly, may report back a plan which may not be feasible, but it seems to his Committee that the principle of adding to the College requirements in some such way should be most carefully studied and a detailed plan submitted.

Dr. Charles F. Martin, Chairman of the Committee on Finance, presented the report of that Committee, including the presentation of the operating statements for 1933, the budgets for 1934 and certain adjustments to provide for necessary additional appropriations to cover the Research Fellowship to be established by the College, the preparation of the John Phillips Memorial Medal and certain salary adjustments of employees. A part of the report follows:

"The Finance Committee, in submitting the detailed statement of the receipts and expenditures for 1933, as also the budget for 1934, is pleased to be enabled to report a very sound condition of the finances of the College. It desires further to express its satisfaction and appreciation of the successful financial operations as conducted by the Executive Secretary's Office, and by the officers associated with the ANNALS OF INTERNAL MEDICINE.

"The Finance Committee also recommends to the incoming Finance Committee that following the recommendation of the auditor that securities be separated between those which would be assigned as endowment fund and those which belong to the general fund, and that in the future these lists of securities be kept separate.

"In addition, the Finance Committee also recommends to the incoming Finance Committee that an analysis of the present list of securities be made and that they secure from competent authorities recommendations for any changes that may be desirable for action on the part of the Board of Regents or the Executive Committee."

The recommendations of the Committee on Finance, on motion regularly seconded and carried, was unanimously approved.

Dr. Maurice C. Pincoffs, Editor of the ANNALS OF INTERNAL MEDICINE, reported

briefly on his work as Editor during the past year. He said the number and character of manuscripts coming to the Editor's office have shown certain fluctuations during the past six months. The number of incoming manuscripts fell off sharply during the last three months, averaging not as many as ten a month, which is less than the average number printed in each issue. This state of affairs, however, remedied itself without any action on the part of the Editor, so that he now is well supplied with material for several months to come.

Dr. Pincoffs pointed out that the size of the journal has shown no essential variation in recent months, although its total size for Volume VI, ending June 1933, was slightly larger than any previous volume. He referred the Board of Regents to the analysis of the journal as prepared by the Executive Secretary and appearing among the financial reports, showing that there has been a steady growth in circulation with no recession at any time. With the election of new members to the College at this meeting, the circulation will be again increased.

Dr. Pincoffs, in further referring to the financial report on the ANNALS OF INTERNAL MEDICINE, stated that a new contract with the printer, beginning July 1, 1934, will be at a rate of approximately 10 per cent higher than previously, due to the increased cost entailed by the Code for the Graphic Arts, but that both he and the Executive Secretary recommended to the Board the continuance of the present printer, feeling that the increased cost is entirely justified.

Dr. Pincoffs then reported as Chairman of the Committee on the Annals, which consisted of himself as Editor, Dr. David P. Barr, Dr. O. H. Perry Pepper and Dr. James H. Means. The report of his Committee follows:

"The Committee on Annals recommends that the Committee from the Board of Regents be continued as at present constituted, with its present functions. Those functions, as stated in the original motion that provided for the Committee, are that this Committee shall be especially interested in the general policy of the Annals, its financial setup and its relation to the public. The Committee is also to aid and counsel the Editor in general about the quality of material published in the journal.

"The Committee on the Annals further recommends that the present Editorial Council be dismissed from service, and that there be constituted a Board of Associate Editors, to be composed of at least five members, and that the Editor be given the privilege of nominating to the Board of Regents the membership of this Board of Associate Editors."

Upon motion by Dr. O. H. Perry Pepper, seconded by Dr. David P. Barr, and regularly carried, the report of the Committee on the Annals was adopted.

Dr. Pincoffs then stated that he would like to make the following nominations to the Board of Associate Editors, submitting them to the Board of Regents for their approval. His nominations, not entirely selected from the membership of the Board of Regents, were:

David P. Barr, St. Louis, Mo.
Robert A. Cooke, New York, N. Y.
James H. Means, Boston, Mass.
O. H. Perry Pepper, Philadelphia, Pa.
Gerald B. Webb, Colorado Springs, Colo.

Dr. Pincoffs stated that he had not had an opportunity to communicate with them to determine their willingness to serve, but expressed the wish to have the approval of the Regents for their appointment, if they will serve.

Upon motion by Dr. Bierring, seconded by Dr. Jennings, the nominations of the above Board of Associate Editors were approved.

The appended report of the Treasurer was submitted by Dr. Stroud, copies of the report being distributed to all members of the Board of Regents.

Upon motion made by Dr. James Alex. Miller, seconded and regularly adopted, the report of the Treasurer was received and placed on file.

Dr. William Gerry Morgan, as Chairman of the Committee on the Life Membership Certificate, presented the following report:

"The Committee recommends the preparation of a suitable Life Membership Certificate of the American College of Physicians, and submits herewith the following suggested form:

"LIFE MEMBERSHIP CERTIFICATE
of
THE AMERICAN COLLEGE OF PHYSICIANS

Whereas

has fulfilled the requirements of the By-Laws, Rules and Regulations of the College appertaining to life membership, he is herewith declared a Life Member.

"In witness whereof the seal of the College and the signatures of the proper Officers are hereunto affixed this _____ day of _____, A.D. 19—.

President
Secretary-General"

Adoption of the report was moved by Dr. Musser, seconded by Dr. White and unanimously carried.

Dr. Ernest B. Bradley, Chairman of the Board of Governors, reported briefly on the work of the Board of Governors, and stated that they had raised the question concerning the attitude of the Board of Regents in regard to membership of certain Mexican physicians and internists and members of the medical fraternity in Cuba.

Dr. Bradley said he had consulted the By-Laws and saw no objection to additional members being elected from those countries, provided they meet the requirements.

The Board of Governors recommended to the Board of Regents that some arrangement be made whereby members from Mexico and Cuba could be brought into the College. By referring to the By-Laws, Article IV, Section 1, it was noted that provision is already made for the election of Governors from countries outside of the United States, and, therefore, no action by the Board of Regents was necessary on the recommendation of the Board of Governors.

The Executive Secretary presented a number of communications and special cases dealing with requests for reinstatement, extension of time to qualify for Fellowship, resignations and cases concerning fees and dues.

By resolution regularly adopted, Dr. I. Warner Jenkins, Waco, Texas, was reinstated to Fellowship in the College.

By individual resolutions regularly adopted, the following resignations were accepted:

Fellows:

Lewis W. Elias, Asheville, N. C.
Howard T. Phillips, Wheeling, W. Va.
S. J. Wolfermann, Fort Smith, Ark.

Associates:

James J. Gable, Norman, Okla.
Wallace T. Partch, Oakland, Calif.
L. C. Sams, Dallas, Tex.
Frank E. Sayers, Terre Haute, Ind.

The Executive Secretary presented mimeographed lists of members who are two or more years delinquent, and who are, therefore, subject to being dropped from the rolls of the College, in accordance with the By-Laws, Article XIII, Section 2.

He stated that the list had been reviewed with members of the Board of Governors, and that, after careful consideration, some members of the Board of Governors wished to communicate further with these delinquent members in their districts, and, therefore, suggested the following resolution, which was regularly adopted:

RESOLVED, that all members whose names appear on the delinquent list of two or more years' standing be automatically dropped in accordance with the By-Laws, if, after further notification, their delinquent dues are not paid within the next thirty days.

The Executive Secretary then presented a second list containing the names of Associates who have not qualified for Fellowship in the required period of five years. In several instances the Governors have recommended that the names be dropped, but in other instances Governors have requested extension of the time.

President Piersol expressed the opinion that the By-Laws explicitly state that if an Associate does not qualify for Fellowship within five years, he is automatically dropped.

Upon motion by Dr. Sydney R. Miller, seconded by Dr. Morgan and regularly adopted, it was

RESOLVED, that the provisions of the By-Laws be adhered to, and that any Associates who have failed to qualify for Fellowship be dropped from the roll.

President Piersol announced the receipt of a letter from the Association of Medicine of the French Language of North America, suggesting that a representative of the College be sent to the Congress to be held in Quebec in August.

Upon motion by Dr. Herrick, seconded by Dr. Musser and regularly adopted, it was

RESOLVED, that Drs. Meakins and Martin be the accredited delegates to represent the College.

President Piersol read a communication from Dr. LeRoy S. Peters, Governor of the College for New Mexico, suggesting a succession in meeting dates of certain national societies.

Upon motion by Dr. James Alex. Miller, seconded by Dr. White and regularly adopted, it was

RESOLVED, that the communication of Dr. Peters be referred, without recommendation, to the Committee on Arrangements for the next Clinical Session.

Dr. Meakins read a communication from the Milbank Memorial Fund regarding a study to be made of physicians' incomes for which the Milbank Fund offered to make certain money available for the investigative work.

After a thorough discussion, it was moved by Dr. Sydney R. Miller, seconded by Dr. Warner, and regularly carried that it be

RESOLVED, that the proposal that we coöperate with the Milbank Fund in this economic investigation be declined, as it is foreign to the purposes and policies of the College.

Dr. Pepper suggested that the incoming officers and the Executive Secretary consider the possibility and advisability of a closer spacing of the several meetings of the Regents during the Annual Session, and asked whether the Sunday meeting could not be held on Monday morning.

President Piersol said that the meetings of the Regents had been arranged in such a manner as to conflict as little as possible with the general program, and had been spaced according to the needs for carrying out the requirements of the By-Laws. That is, it is always necessary to have an early meeting of the Board of Regents to take care of elections to membership, and it is also necessary to have a late meeting of the Board of Regents, after the Annual Business Meeting, to care for the reorganization for the new year. The matter, however, shall be referred to the incoming officers for the next year.

PRESIDENT PIERSOL: "Before we adjourn, as this will be the last time when I will have the distinction of presiding over this body, I want to take this occasion to express to you my very sincere appreciation for the help and forbearance you have shown to me during the affairs of the last year."

Adjournment.

AMERICAN COLLEGE OF PHYSICIANS

TREASURER'S REPORT FOR THE YEAR 1933

Gentlemen:

It is with much satisfaction that I am able to report that the College was able to keep within its budget during the year 1933 and end the year with a surplus of \$5,801.06. For this accomplishment we are mainly indebted to our Executive Secretary. This is especially true when we consider that for the year 1933 dues were reduced approximately 25 per cent and the number of incoming Fellows was limited through the change in the By-Laws requiring new candidates to be presented first for Associateship.

The cash balance on December 31, 1933 was \$55,545.82, of which \$11,900.00 still remains in closed banks in Pittsburgh. We believe, on good authority, in time all of this money will accrue to the College.

The resources of the College as of December 31, 1933 amount to \$123,987.03. Of this \$54,010.00 is in the endowment fund and \$69,977.03 in the general fund. Our investments as of December 31, 1933 cost \$63,675.01. These securities were valued on April 16, 1934 at \$62,726.00.

During January 1934, upon authorization of the Board of Regents, and with the approval of the Finance Committee, twenty United States Government $4\frac{1}{4}$'s— $3\frac{1}{4}$'s bonds and five Dominion of Canada 4's bonds were purchased from our general fund so that our total investments to date are valued at \$87,726.00.

Based upon the receipts for January and February 1934, and the attendance at the 18th annual session with the large number of exhibitors, and considering the number of new Fellows elected, it is the opinion of your Treasurer that the College can be financially maintained within the estimated budget of \$52,610.50 for the year 1934 and that our income will be more than adequate.

At the request of your Treasurer Mr. Loveland has made an analysis of our financial situation as of December 31, 1933. Such an analysis follows.

Respectfully submitted,

(Signed) WILLIAM D. STROUD,
Treasurer

THE AMERICAN COLLEGE OF PHYSICIANS

FINANCIAL ANALYSIS

1933

To the Board of Regents:

The auditor's report of his examination of the accounts of the College is hereto attached. The statements disclose a surplus of \$5,801.06, of which \$5,266.06 was added to the General Fund and \$535.00 was added to the Endowment Fund. Our estimated surplus at the beginning of the year, as submitted to the Board of Regents, was \$5,142.50, which is \$658.56 less than the actual surplus. Although the budget for 1933 was closely limited, the business of the College was not only carried on within the budget but with a little to spare.

The surplus for the previous year, 1932, was \$10,598.08. However, for the year 1933, it is proper to point out that the income was greatly reduced for the following reasons:

(1) Dues were reduced approximately 25 per cent.

(2) The change in the By-Laws, requiring new candidates to be presented first for Associateship, has greatly reduced the number of possible candidates for Fellowship for 1933, with the consequent reduction in the income from initiation fees. Whereas the 1931 income from Fellowship initiation fees amounted to \$18,365.00, the income from that source for 1933 amounted only to \$2,856.68. Due to an increasing number of Associates becoming eligible for advancement to Fellowship, it is believed that the income from initiation fees will increase in the future.

(3) During 1933, the Board of Regents held no meeting between the Montreal Clinical Session and December 3. The new members elected on December 3 came into the College as of January 1, 1934, so far as fees and dues were concerned, for it would not have been seemly to charge them dues for 1933 which was practically at an end.

(4) Financial stringencies of the times were responsible for a reduction in the number who subscribed to life membership. For illustration, in 1931 income from subscriptions to life membership amounted to \$2,400.00, in 1930 to \$3,100.00, whereas the amount received for 1933 was only \$535.00.

(5) Income from bonds and income from interest on bank balances have been reduced due to default by the City of Detroit on \$2,000.00 of bonds we own and due to banks discontinuing to pay any interest whatsoever on bank balances on deposit since the bank holiday in March 1933.

The ANNALS OF INTERNAL MEDICINE shows a distinctly improved financial condition. Our printing costs were very materially reduced after the new printers were selected, beginning July 1933. These advantageous prices still obtain, but there is a possibility of increased costs due to the N. R. A. code for the graphic arts. The income from subscriptions fell off during 1933 due to expirations of direct subscriptions (non-member subscriptions) which we could not renew, presumably due to economic conditions. The income from advertising, though very slightly higher than for 1932, is the largest in the history of the Annals.

During 1933, \$8,000.00 (par value) in securities were matured, and \$6,097.50 reinvested in securities. The total holdings in securities, all bonds, on December 31, 1933, amounted to \$63,675.01.

The cash balance on December 31, 1933, was \$55,545.82, of which \$11,900.00 remained in closed banks. During 1933, \$6,411.79 was repaid by closed banks.

A condensed comparison of income and expenditures for 1932 and 1933 follows:

General Fund

<i>Income</i>	1932	1933
Annual Dues	\$27,718.00	\$20,069.80
Initiation Fees	10,275.00	2,856.68
Income from Endowment Fund	2,365.79	1,360.66*
Income from Other Securities	540.64	616.66
Interest on Bank Balances	381.16	243.28
Other Miscellaneous Income	396.81	269.11
	<u>\$41,677.40</u>	<u>\$25,416.19</u>

Expenditures

Annual Clinical Session (San Francisco)			
Total Expenses	\$18,094.16		
Less Income from			
Exhibits	\$4,609.73		
Guest Fees	875.00	5,484.73	\$12,609.43
Annual Clinical Session (Montreal)			
Total Expenses	\$10,820.58		
Less Income from			
Exhibits	\$4,192.21		
Guest Fees	374.50		
Banquet Balance	293.32	4,860.03	\$ 5,960.55

* For 1933, the cost of awarding the Phillips Memorial Prize was deducted from the income from the Endowment Fund. This was not done for 1932; hence, the variance in amount.

ANNALS OF INTERNAL MEDICINE (1932)

Income

Subscriptions	18,062.13	
Advertising	4,536.84	22,598.97
Total Cost	<u>22,402.70</u>	— 196.27*

ANNALS OF INTERNAL MEDICINE (1933)

Income

Subscriptions	17,785.81	
Advertising	4,540.20	22,326.01
Total Cost	<u>19,540.36</u>	— 2,785.65*

Executive Secretary's Office (Including College Headquarters, Committees, Regents)	17,299.02	14,805.02
Directory (Supplement only for 1932)	727.19	1,614.00
Miscellaneous	527.62	556.21
	<u>\$32,054.32</u>	<u>\$20,150.13</u>

Endowment Fund

Life Membership Fees	\$ 975.00	\$ 535.00
----------------------------	-----------	-----------

Your Executive Secretary's office has been conducted conservatively. Expenditures have been curtailed wherever possible. The office staff was reduced to two assistants for the latter part of 1933. A further reduction in the rental of the College headquarters has been obtained, beginning February 1, 1934.

The budgets herewith submitted for 1934 have been carefully estimated.

Respectfully submitted,

(Signed) E. R. LOVELAND,
Executive Secretary

April 15, 1934.

AMERICAN COLLEGE OF PHYSICIANS, INC.

BALANCE SHEET, DECEMBER 31, 1933

Assets

Cash:

In Banks and on Hand	\$43,645.82	
In Closed Banks:		
Bank of Pittsburgh	\$5,847.87	
Exchange National Bank, Pittsburgh	2,040.74	
Highland National Bank, Pittsburgh	4,011.39	11,900.00
		<u>\$ 55,545.82</u>
Accounts Receivable		207.90
Investments at cost, as annexed		63,675.01
Accrued Interest on Investments		911.55
Inventory of Keys, Pledges and Frames, at cost		319.96
Deferred Expenses, 18th Annual Clinical Session		2,436.27
Furniture and Equipment, at cost	3,882.15	
Less, Allowance for Depreciation	1,992.60	1,889.55
		<u>\$124,986.06</u>

Liabilities

Deferred Income:

Advance Collections for Exhibits, Eighteenth Annual Clinical Session	\$ 577.97	
Advance Subscriptions for Volumes VIII and IX, ANNALS OF INTERNAL MEDICINE	421.06	999.03
		<u>\$123,987.03</u>

* Profit.

Funds

Endowment Fund, as annexed	\$54,010.00	
General Fund, as annexed	<u>69,977.03</u>	<u>\$123,987.03</u>

General Fund

For the Year ended December 31, 1933

Balance, December 31, 1932	\$64,810.97	
Less:		
Transfer to Endowment Fund of the Initiation Fee of one new Life Member	100.00	
	<u>\$64,710.97</u>	
Add:		
Net Income for the year, as annexed	5,266.06	
Balance, December 31, 1933	<u>\$69,977.03</u>	

Endowment Fund

For the Year ended December 31, 1933

Principal Account:		
Balance, December 31, 1932	\$53,375.00	
Add:		
Life Membership Fees received during 1933	535.00	
Transfer of Initiation Fee of one new Life Member from General Fund	100.00	
Balance, December 31, 1933	<u>\$54,010.00</u>	
Income Account:		
Income from Securities (Endowment Fund only)	\$ 2,385.86	
Less:		
Award of the John Phillips Memorial Prize and expenses of the recipient incident thereto	1,025.20	
Balance, Transferred to Operations for the Period	<u>\$ 1,360.66</u>	

INCOME AND EXPENSES

For the Year ended December 31, 1933

Income

Annual Dues	\$20,069.80	
Initiation Fees	2,856.68	
Income from Endowment Fund (Net, after deducting Phillips Prize)	1,360.66	
Income from other Securities	616.66	
Interest on Bank Deposits	243.28	
Profit from Sale of Keys, Pledges and Frames	137.38	
Profit, Credit Balance on Foreign Exchange (net)	126.12	
Receipts from 1931-32 Directory	1.75	
Profit on Maturities of Securities (net)	2.96	
Receipts from Annals of Clinical Medicine90	\$25,416.19

Expenses

Seventeenth Annual Clinical Session

Income:

Exhibits (net)	\$ 4,192.21	
Guest Fees	374.50	
Banquet Profit	<u>293.32</u>	4,860.03

Expenses:

Salaries	2,937.02	
Communications (Postage, Telephone, etc.)	443.95	
Office Supplies and Stationery	<u>64.24</u>	
Forward	3,445.21	4,860.03

ABRIDGED MINUTES OF BOARD OF REGENTS

Brought Forward	3,445.21	4,860.03
Printing	1,222.82	
Traveling Expenses	4,076.69	
Miscellaneous:		
Advertising	\$ 148.00	
Badges	339.85	
Ladies Committee	256.35	
Presidential Reception	195.00	
Smoker	228.00	
Rental of Equipment	227.68	
Reporting	252.94	
Scientific Exhibits	101.99	
Other Miscellaneous Items	326.05	2,075.86
Net Expenses of Clinical Session		5,960.55

ANNALS OF INTERNAL MEDICINE

Income:

Subscriptions:

Volume I	10.85	
" II	6.85	
" III	13.85	
" IV	22.05	
" V	34.18	
" VI	912.64	
" VII	16,785.39	17,785.81

Advertising (net)

Volume VI	2,317.26	
" VII	2,222.94	4,540.20
		22,326.01

Expenses:

Salaries	\$ 4,940.51	
Communications (Postage, Telephone, etc.)	959.66	
Office Supplies and Stationery	245.23	
Printing	13,227.45	
Traveling Expenses	41.40	
Miscellaneous	126.11	19,540.36

Net profit on ANNALS OF INTERNAL MEDICINE 2,7

Total Income \$28,2

Executive Secretary's Office

Expenses:

Salaries	\$ 8,118.86	
Communications (Postage, Telephone, etc.)	1,548.32	
Office Supplies and Stationery	328.47	
Printing	170.91	
Rent and Maintenance	2,889.77	
Traveling Expenses	1,190.25	
Annual Audit	200.00	
Fee to Custodian of Securities	94.86	
Miscellaneous	263.58	14,805.02

ANNALS OF INTERNAL MEDICINE

Distributed Free to Life Members	168.00	
1933 Directory	1,614.00	
Depreciation on Furniture and Equipment	388.21	22,9

Net Income for the Year Ended December 31, 1933 \$ 5,2

INVESTMENTS

December 31, 1933

Par Value	Bonds	Cost
\$ 4,000	Canadian National Railway, 4½s, 1956	\$ 3,930.00
5,000	Canadian National Railway, 5s, July 1, 1969 }	7,042.50
2,000	Canadian National Railway, 5s, Oct. 1, 1969 }	
2,000	Canadian National (West Indies), SS. Co., 5s, 1955	2,040.00
2,000	City of Covington, Ky., 4¾s, 1946	2,134.01
2,000	City of Detroit, Mich., Lighting, 4¾s, 1944	2,010.40
2,000	City of Detroit, Mich., Street Ry., 4¾s, 1949	2,025.26
2,000	City of Houston, Texas, School District, 4¾s, 1942	2,077.50
2,000	City of Los Angeles, Calif., Sewage Disposal "B," 5s, 1943	2,158.24
1,000	City of Montreal, Canada, 5s, 1956	1,071.30
2,000	City of Newark, N. J., Series 2, 4½s, 1944	2,075.00
10,000	City of Philadelphia, Pa., 4½s, 1949-79	10,225.00
2,000	City and County of San Francisco, Calif., Fire Protection, 5s, 1941	2,137.12
2,000	City of Seattle, Wash., Light and Power, 4¾s, 1957	1,995.00
2,000	City of Toronto, Canada, Local Improvement, deb. 5s, 1936	2,020.00
500	Oklahoma Gas and Electric Co., deb. 6s, Series "A," 1940	487.50
2,000	Port of New York Authority, Interstate Bridge, Series "B," 4½s, 1952	2,042.20
2,000	Port of New York Authority, Interstate Tunnel, Series "E," 4½s, 1958	2,065.40
2,000	Province of Alberta, Canada, deb. 4½s, 1956	1,896.00
2,000	Province of Ontario, Canada, deb. 4½s, 1942	2,015.00
1,000	Province of Ontario, Canada, deb. 5s, 1942	1,052.26
2,000	U. S. Treasury, 4s, 1944-54	1,998.13
9,000	U. S. 4th Liberty Loan, 4½s, 1938	9,177.19
<u>\$62,500</u>	Total (Annual Yield, 4.47%)	<u>\$63,675.01</u>

ABRIDGED MINUTES OF THE BOARD OF REGENTS

CHICAGO, ILLINOIS

April 20, 1934

The third meeting of the Board of Regents of the American College of Physicians met and was called to order in the Palmer House, Chicago, Ill., at 12:40 o'clock, President Jonathan C. Meakins presiding.

The following were present: Dr. Jonathan C. Meakins, Dr. James Alex. Miller, Dr. James H. Means, Dr. William D. Stroud, Dr. William Gerry Morgan, Dr. George Morris Piersol, Dr. William J. Kerr, Dr. G. Gill Richards, Dr. David P. Barr, Dr. Arthur R. Elliott, Dr. Clement R. Jones, Dr. S. Marx White, Dr. Francis M. Pottenger, Dr. Luther F. Warren, Dr. Ernest B. Bradley, Dr. Maurice C. Pincoffs, and Mr. E. R. Loveland, Executive Secretary.

Mr. Hennessey of the Chicago Association of Commerce expressed the appreciation of his organization to the College for holding its Annual Session in Chicago.

President Meakins spoke briefly of his plans for the period of his Presidency, expressing the hope that the work might be carried on successfully and that he might have the coöperation and aid of the Board of Regents. He welcomed to the Board a new member, Dr. G. Gill Richards, who had been elected at the General Business Meeting of the preceding day.

Upon motion regularly seconded and adopted, the reading of the Minutes of the previous meeting was dispensed with.

Upon motion by Dr. White, seconded by Dr. Barr and regularly carried, it was RESOLVED, that Dr. William D. Stroud be reelected as Treasurer for 1934-35.

Upon motion by Dr. White, seconded by Dr. Bradley and regularly carried, it was RESOLVED, that Dr. William Gerry Morgan be reelected as Secretary-General for 1934-35.

Upon motion by Dr. Barr, seconded by Dr. Bradley and regularly carried, it was RESOLVED, that the following members be elected to the Executive Committee:

Walter L. Bierring, Des Moines, Iowa
 James H. Means, Boston, Mass.
 Maurice C. Pincoffs, Baltimore, Md.
 Francis M. Pottenger, Monrovia, Calif.
 Roger I. Lee, Boston, Mass.

These elected members, with the President, President-Elect, Secretary-General and Treasurer constitute the Executive Committee for 1934-35.

Upon motion by Dr. Means, seconded by Dr. Morgan and regularly carried, it was RESOLVED, that Dr. George Morris Piersol serve as a member of the Committee on Credentials for three years.

President Meakins made the following appointments to committees:

Committee on Finance

Roger I. Lee (to serve until 1937)

The Finance Committee for 1934-35 is composed of the following:

Charles F. Martin, Chairman, Montreal, Que.

James Alex. Miller, New York, N. Y.

Roger I. Lee, Boston, Mass.

Committee on Public Relations

James F. Churchill (to serve until 1938)

Ernest B. Bradley (to serve until 1936)

The Committee on Public Relations for 1934-35 consists of:

James Alex. Miller, Chairman, New York, N. Y.

Ernest B. Bradley, Lexington, Ky.

James F. Churchill, San Diego, Calif.

Charles G. Jennings, Detroit, Mich.

Ex Officio

Jonathan C. Meakins, Montreal, Que.

Committee on Annals of Internal Medicine

O. H. Perry Pepper (to serve until 1937)

The Committee on ANNALS OF INTERNAL MEDICINE for 1934-35 consists of:

Maurice C. Pincoffs, Chairman, Baltimore, Md.

David P. Barr, St. Louis, Mo.

James H. Means, Boston, Mass.

O. H. Perry Pepper, Philadelphia, Pa.

Committee on the John Phillips Memorial Prize

David P. Barr, Chairman, St. Louis, Mo.

Arthur R. Elliott, Chicago, Ill.

O. H. Perry Pepper, Philadelphia, Pa.

James H. Means, Boston, Mass.

William J. Kerr, San Francisco, Calif.

Committee on Constitution and By-Laws

Alfred Stengel (to serve until 1937)

The Committee on Constitution and By-Laws for 1934-35 consists of:

Sydney R. Miller, Chairman, Baltimore, Md.

Francis M. Pottenger, Monrovia, Calif.

Alfred Stengel, Philadelphia, Pa.

President Meakins stated that he would make appointments to the Committee on Nominations within the period of one month, as required by the By-Laws.

The Executive Secretary was called upon to present invitations for the 1935 Annual Clinical Session. Chief invitations were from Philadelphia and Indianapolis.

Upon motion by Dr. Pottenger, seconded by Dr. Morgan and regularly carried, it was RESOLVED, that the 1935 Annual Session be held in Philadelphia.

President Meakins presented a set of resolutions submitted by the Council of the Chicago Medical Society pertaining to the exploitation of drugs, preparations, patent medicines, etc., over the radio, and petitioning the Federal Radio Commission to exercise authority in the interest of the health of the citizens of the United States.

Dr. Morgan stated that the Radio Commission in Washington has offered the criticism that they cannot take any steps limiting the nature of drugs that may be broadcast over the radio because of insufficient backing; if they had the whole-hearted backing of a greater section of the interested public, they would be in a position to do something more effective about the matter of restricting national broadcasts concerning patent medicines, drugs and other preparations.

Dr. Morgan stated that if it is not inconsistent with the objects of the College, it would seem to him a helpful step in the right direction if suitable resolutions were drawn, offered and passed and forwarded to this Commission.

Dr. Pincoffs suggested that the Board should look carefully into the wording of what we are asked to support, inasmuch as he did not feel the College should go on record as being opposed to the principle that all advertising of remedies should be barred from the air, if the advertising of remedies is not to be barred from the press. He stated that there is a bill before Congress in which very stringent regulations and penalties are laid down for any advertising, air or press, which would be unfair or make statements which could not be substantiated. Rather than barring these advertisers from the air, Dr. Pincoffs expressed the opinion that the College should throw its support in favor of the regulation of what they may say and of penalizing them for statements which may be considered to be unsupportable.

After further discussion by Dr. James Alex. Miller and Dr. White, the following resolution was regularly adopted:

RESOLVED, that the set of suggested resolutions submitted by the Council of the Chicago Medical Society pertaining to the exploitation of drugs, preparations, patent medicine, etc., over the radio and petitioning the Federal Radio Commission to exercise authority in the interest of the health of the citizens of the United States, be referred to the Committee on Public Relations, with the suggestion that the burden of this matter be placed on the American Medical Association, primarily to determine what their policy is, and to coöperate with them if they desire the support of the College, with power to act on the part of the Committee.

President Meakins appointed Dr. James Alex. Miller to act as Chairman of the Public Relations Committee for 1934-35.

Upon motion by Dr. White, seconded by Dr. Kerr and regularly carried, it was

RESOLVED, that Dr. Alfred Stengel of Philadelphia be elected as General Chairman of the 1935 Annual Clinical Session.

DR. PINCOFFS: "I wish to take this opportunity of bringing before the Regents, and especially the Committee on Credentials, a point which has appealed to me in connection with their task of revising our requirements for elevation from Associateship to Fellowship.

"It has seemed to me that in that step lies perhaps one of the most potentially important influences of the College, and that it might be aided to become such if the principle were adopted that the position of Regent or of Governor in this College carried with it an obligation to assist the Associates by counsel and perhaps by providing opportunities, directly or indirectly, in so adding to their professional equipment that they might pass these newer and higher requirements. It would not only, I think, be of great assistance to many of the younger Associates to have the feeling that they had a right to appeal to our Governors and to our Regents for that purpose, but, also, it would help to bring together in a certain community of effort, in some of the cities and some of the sections of the country, the members of the College at times of the year other than when we meet here together in these annual sessions."

DR. BARR: "I was very much impressed when we were in Southern California at the apparent cohesion of the group in Southern California. I think Dr. Pottenger might tell us something about how that has been accomplished."

DR. POTTENGER: "Our group out there have worked together very nicely. We have on one or two occasions had meetings where we got together for some special occasion and had visitors come. That has helped us very, very much. Dr. Crispin as the Governor and myself as the Regent always advise young men who are coming up as to what to do. We have had a great many young men who appealed to us and wanted to know what to do. We would immediately get them busy in medical societies and in their studies and in their teaching and try to help them in looking toward membership in this organization. If they were not prepared, we would advise them not to make application until they had done something worth while."

DR. KERR: "The suggestion made by Dr. Pincoffs strikes me as a very fine one. I feel that that is one of the avenues for further development which we must foster.

"Perhaps it is not inappropriate to consider still another avenue for use in the future. It seems to me that one of the great needs in our country today is to take some of the modern medical thought and practice to the byways and crossroads. In the smaller communities, at least in our part of the country, perhaps also in others, some very poor medicine is being practiced, men making use of so-called technical methods of diagnosis which are improperly done and improperly interpreted. Most of these men who are in general practice do not have the opportunity to get away to meetings of this sort or to meetings of the American Medical Association, chiefly because they cannot afford to leave. They stand alone in their community.

"It seems to me that perhaps some time we may take up the question of the development of postgraduate education, which, through our Regents and Governors and Fellows and medical schools generally throughout the country, may be taken to these doctors at the crossroads. I think there is the weakest place in our whole system, at least in this country. As an extension of the idea which Dr. Pincoffs has expressed, this might be considered and worked out."

DR. RICHARDS: "Just recently they had a sectional meeting of the American College of Surgeons in Salt Lake City, as they do all over the country. It was such a huge success that I have often wondered if at some time in the near future we should not consider something of that sort. As an example, they had some six or eight visiting men of prominence at this meeting, and it attracted the largest group of medical men in the Intermountain region of any meeting we have ever had. They held clinics and afternoon and evening sessions, much as we do here. We saw doctors from the small, outlying districts that we had never seen at our state meetings. In addition to that they held one large public meeting. I have never seen so many members of the laity interested in an affair of medicine. Our large auditorium, the Tabernacle, which seats about 10,000 people, was crowded to the utmost, and they had additional meetings in another large hall.

"It seems to me that we could take an initiative along that line and follow their example to great advantage."

PRESIDENT MEAKINS: "Personally, in the last ten years I have had a great deal to do with what one might call extension postgraduate medical education. I think I have crossed the Continent from Halifax to Victoria five times on such tours.

"I feel very strongly, from personal experience, that the men in the highways and at the crossroads are thirsty to meet and see and hear men who will bring to them something of almost a missionary spirit of modern medicine."

Upon motion by Dr. Pottenger, seconded by Dr. Jones and regularly carried, it was RESOLVED, that the President appoint a Committee to investigate the advisability of and to formulate plans for the closer organization and greater cohesion of our members in their particular communities or states, such as done by the American College of Surgeons through their sectional meetings, with the object of carrying extension postgraduate medical educational facilities to physicians in more remote locations, and to bring back a report at the next meeting of the Board of Regents.

Upon motion by Dr. White, seconded by Dr. Piersol, it was

RESOLVED, that the date of the next meeting be referred to the Executive Committee, with power to act and to determine the date of meeting within thirty days.

Dr. Barr suggested that inasmuch as so many members of the College attend the meeting of the Association of American Physicians at Atlantic City, which will be held toward the end of April, the meeting of the College might be arranged the week preceding that of the Association of American Physicians.

Dr. Richards of Salt Lake City also asked that the Executive Committee keep in mind that physicians are busiest during the winter months, and it would be much more convenient for them to get away toward spring than during the midwinter months.

President Meakins expressed the consensus of opinion of the Board of Regents that a meeting toward the end of April or at least during April would be preferable.

It was requested that the Executive Committee, in selecting the date for the meeting, take into consideration the above suggestions and also definitely provide against any conflict with the date of the meeting of the American Medical Association.

Adjournment.

Attest: E. R. LOVELAND,
Executive Secretary

President Meakins, on May 5, 1934, appointed the following Committees:

Committee on Nominations

Charles F. Martin, Chairman, Montreal, Que.
Roger I. Lee, Boston, Mass.
William J. Kerr, San Francisco, Calif.
Charles Hartwell Cocke, Asheville, N. C.
Gerald B. Webb, Colorado Springs, Colo.

Committee on Extension of Postgraduate Education

Francis M. Pottenger, Chairman, Monrovia, Calif.
John H. Musser, New Orleans, La.
Luther F. Warren, Brooklyn, N. Y.
Ernest B. Bradley, Lexington, Ky.
Walter L. Bierring, Des Moines, Iowa

MINUTES OF THE BOARD OF GOVERNORS

CHICAGO, ILLINOIS

April 16, 1934

The Board of Governors of the American College of Physicians met and was called to order in the Palmer House, Chicago, Ill., at 5:10 o'clock, by the Chairman, Dr. Ernest B. Bradley, Lexington, Ky.

The Executive Secretary called the roll and the following Governors were present: Dr. Fred W. Wilkerson, Dr. Lewis B. Flinn, Dr. Turner Zeigler Cason, Dr. Russell H. Oppenheimer, Dr. Ernest B. Bradley, Dr. G. W. F. Rembert, Dr. Louis H. Fligman, Dr. Robert A. Cooke, Dr. A. B. Brower, Dr. T. Homer Coffen, Dr. Charles T. Stone, Dr. Rock Sleyster, Dr. Egerton L. Crispin, Dr. James G. Carr, Dr. Ernest E. Laubaugh, Dr. Samuel E. Munson, Dr. Robert M. Moore, Dr. Thomas T. Holt, Dr. Roger I. Lee, Dr. Adolph Sachs, Dr. John O. Manier, Dr. Jabez H. Elliott, Dr. Oliver C. Melson, Dr. Tom Bentley Throckmorton, Dr. Joseph E. Knighton, Dr. Edward L. Tuohy, Dr. A. Comingo Griffith, Dr. Clarence L. Andrews, Dr. Chas. Hartwell Cocke, Dr. Julius O. Arnson, Dr. Alexander M. Burgess, Dr. J. Morrison Hutcheson, Dr. G. Gill Richards, and Dr. A. B. Chase, proxy for Dr. Lea A. Riely, and Mr. E. R. Loveland, Executive Secretary.

The following memorial was presented by Dr. Cocke:

"In the death of Dr. W. Blair Stewart, the American College of Physicians has suffered the loss of a loyal, devoted Fellow. As Chairman of the Board of Governors he rendered valuable and exceptional service. Enthusiastic but ever courteous, zealous always for the best interests of the College, a presiding officer of great fairness and thoughtfulness, he endeared himself to the body over which he presided with dignity and distinction.

"In his passing, the Board of Governors wishes to pass this minute of respect to the memory of its presiding officer for more than four years and orders that it be spread upon its minutes."

On motion made by Dr. Cocke and seconded by Dr. Griffith, the resolution was adopted by a rising vote.

Upon motion made by Dr. Moore, and seconded by Dr. Cocke, the reading of the Minutes of the last meeting was dispensed with.

The Executive Secretary stated he had communications from several Governors expressing inability to attend the meeting.

Chairman Bradley announced that it was the desire of the Committee on Credentials that the Governors exercise care in selecting as Associates men who will qualify as Fellows.

The Executive Secretary reported the following new Life Members since January 1, 1934:

Samuel E. Thompson, Kerrville, Tex.
 Philip H. Jones, New Orleans, La.
 Philip I. Nash, Brooklyn, N. Y.
 E. Moore Fisher, Washington, D. C.
 Frederick O. Fredrickson, Chicago, Ill.
 Jabez H. Elliott, Toronto, Ont.

The Executive Secretary reported that the membership, following elections by the Board of Regents on April 15, is now approximately 3,095, consisting of

5 Masters
 2347 Fellows
 743 Associates

The number of men elected to Fellowship, of necessity, has decreased materially since the By-Laws were amended in 1929, requiring new members to serve an Associateship of three to five years before becoming eligible for Fellowship.

The Executive Secretary then presented a list of all members delinquent for a period of two or more years, asking each member of the Board of Governors to carefully go over the list for his territory and to give definite recommendations, if not immediately ready, within thirty days, when those still delinquent would be dropped in accordance with the provisions of the By-Laws. Every man whose name appeared on the delinquent list had been notified on a number of occasions, and so far as the Executive Offices are concerned, it was felt that this limited number of members had probably lost interest and were willing to have their names discontinued on the roll.

The Executive Secretary presented an appended list of Associates, whose term of Associateship expired with the Chicago meeting, but who had failed to qualify for Fellowship in accordance with the requirements of the By-Laws. The Board of Governors were asked individually to examine this list and make any special recommendations, in case they knew of adequate reasons why these Associates had failed to present the credentials for Fellowship.

Dr. A. Comingo Griffith, Governor for Missouri, made the recommendation that the College send out an extra supply of programs of the Annual Clinical Sessions to different cities, so that these programs could be placed in the doctors' rooms at the various hospitals, so that a larger number of physicians could be informed about our annual meetings. It is desirable to have physicians see what the meetings of the College are about and what class of men are on the programs.

Dr. Charles T. Stone, Governor for Texas, reported that two distinguished physicians on the staff of the National University of Mexico, had been presented and elected to Fellowship at this meeting. He said that these two men have done very signal work in Mexico in raising the standards of medical education there. It is an excellent opportunity for the College to begin to extend its influence into Mexico in a way that will be helpful not only to the internists of Mexico, but to the College. He inquired as to the desirability of having official representation on the Board of Governors from Mexico.

Dr. Turner Z. Cason, Governor for Florida, reported that there are several excellent men in Florida who are not easily interested in the College, primarily because they feel that Florida is more or less of an orphan, for the College meetings are always held in midwinter, or very early spring. He inquired whether there are likely to be some regional meetings that might be held in such sections to further interest such physicians.

Dr. Cason further reported that there are a number of good physicians in Cuba who would be interested in the organization, and who would be eligible for membership.

Chairman Bradley reported that we already have a number of men in Puerto Rico, and that he would be glad to consult the Board of Regents concerning the extension of College activities to Mexico and Cuba. He expressed the opinion that it would be advantageous to have some of the outstanding men from any or all of the adjacent countries, provided they were not too far removed to attend some of the College meetings.

Dr. Bradley also reported that the Board of Regents had never taken official action on the matter of regional meetings, it being felt in the past that a large, eminently successful meeting was more to be desired than several smaller, less important meetings.

Upon motion by Dr. Cason, seconded by Dr. Cocke and regularly carried, it was

RESOLVED, that the Board of Governors recommend to the Board of Regents that they consider the question of accepting members from Cuba and Mexico.

Dr. Robert Moore, Governor for Indiana, spoke briefly concerning an occasional candidate who is approved by a Governor but rejected by the Committee on Credentials and no detailed report covering the reasons for rejection being transmitted to the Governor. He expressed the opinion that full details underlying rejection should be transmitted in all cases to the Governor.

The Executive Secretary reported that the Committee on Credentials does not record officially their reasons for rejecting a candidate, other than by checking the column indicating "not qualified." It is, therefore, often impossible for him to report in detail to a Governor the reason why the Committee on Credentials voted adversely on a candidate.

Chairman Bradley requested the Executive Secretary to take up the particular case to which Governor Moore referred with the Committee on Credentials.

Adjournment.

Attest: E. R. LOVELAND,
Executive Secretary

MINUTES OF THE BOARD OF GOVERNORS

CHICAGO, ILLINOIS

April 19, 1934

The second meeting of the Board of Governors of the American College of Physicians met and was called to order in the Palmer House, Chicago, Ill., at 5:35 o'clock, Chairman Bradley presiding.

The Executive Secretary called the roll and the following Governors were present: Dr. Fred W. Wilkerson, Dr. Turner Zeigler Cason, Dr. William R. Houston, Dr. James G. Carr, Dr. Ernest B. Bradley, Dr. G. W. F. Rembert, Dr. Louis H. Fligman, Dr. A. B. Brower, Dr. T. Homer Coffen, Dr. Charles T. Stone, Dr. Egerton L. Crispin, Dr. Ernest E. Laubaugh, Dr. Samuel E. Munson, Dr. Adolph Sachs, Dr. John O. Manier, Dr. G. Gill Richards, Dr. Jabez H. Elliott, Dr. Oliver C. Melson, Dr. Joseph E. Knighton, Dr. A. Comingo Griffith, Dr. Clarence L. Andrews, Dr. Chas. Hartwell Cocke, Dr. Alexander M. Burgess, Dr. J. Morrison Hutcheson, and Mr. E. R. Loveland, Executive Secretary.

Dr. George Morris Piersol, the retiring President of the College, appeared before the Board of Governors to thank them for their aid and cooperation during the past year, particularly in connection with the selection and checking up of candidates. Their aid to the

Committee on Credentials had been exceedingly helpful, because the great responsibility in selecting candidates lies on individual members of the Board of Governors. It would be utterly impossible for the Committee on Credentials to obtain the necessary information about candidates without the aid of the Governors.

Dr. Piersol especially requested the Board of Governors to make an effort not only to see that accurate information is furnished the Committee on Credentials about candidates, but that they expend every effort to see that the proper sort of candidates for Associateship in the various districts are proposed. He pointed out that the Constitution and By-Laws provide that only men of exceptional and outstanding qualifications, particularly men whose age is beyond that where it is dignified for them to be Associates, may be proposed directly for Fellowship. In exercising this right, members of the Board of Governors should bear in mind that the Constitution particularly refers to "men of outstanding attainments and ability," and the Committee on Credentials cannot entertain proposals directly for Fellowship of other than such candidates. It is futile, as well as embarrassing, to propose men directly for Fellowship who have not attained the distinction to which that class of membership entitles them.

Upon motion by Dr. Stone, seconded by Dr. Griffith, and regularly carried, it was RESOLVED, that Dr. Ernest B. Bradley be elected as Chairman of the Board of Governors.

Upon motion by Dr. Griffith, seconded by Dr. Brower, and regularly carried, it was RESOLVED, that Dr. Charles Hartwell Cocke be elected as Vice Chairman of the Board of Governors.

Chairman Bradley, before adjourning the meeting, invited members of the Board of Governors to communicate with him, or with President Meakins, concerning any suggestions for the conduct of the next meeting. Sometimes men in the audience get a better idea of those things on the program that please the doctors than the man on the platform does. Some recommend longer papers and a fewer number.

Dr. Bradley commended the Board for its large attendance at this meeting.

Adjournment.

Attest: E. R. LOVELAND,
Executive Secretary

MINUTES OF THE GENERAL BUSINESS MEETING

CHICAGO, ILLINOIS

April 19, 1934

The Annual General Business Meeting of the American College of Physicians met and was called to order in the Palmer House, Chicago, Ill., at 5:05 o'clock, President Piersol presiding.

The Executive Secretary read an abstract of the Minutes of the meeting held in Montreal on February 9, 1933. Upon motion made by Dr. Cocke, regularly seconded and carried, the Minutes were approved.

Dr. William Gerry Morgan presented his report as Secretary-General of the College, stating that most of the facts relating to his report had already been given by the President in his address at the Convocation on Wednesday evening. He expressed the opinion that members might look forward with a great deal of gratification and courage to the immediate future of the College. The membership has increased in spite of rather heavy losses by death and restrictions in the membership requirements.

Upon motion by Dr. Jones, regularly seconded and carried, the report of the Secretary-General was accepted and placed on file.

Dr. William D. Stroud presented his annual report as Treasurer, which will also be found published in the Minutes of the Board of Regents.

Upon motion by Dr. Griffith, seconded by Dr. Cocke and carried, the Treasurer's report was accepted and placed on file.

Mr. E. R. Loveland presented the report of the Executive Secretary for the year, covering the registration at this Clinical Session, which is second only to the Clinical Session held in Baltimore in 1931. He pointed out that the membership statistics had been given by the Secretary-General, and the report on finances by the Treasurer. During the past year a new Directory had been published and the regular work of the College Headquarters had been carried on as economically as possible, but not to such an extent as to interfere with or harm the work of the organization. He reported that the Annals has greatly improved from a financial standpoint, due in part to reduced printing costs through a new printer, and in part to the excellent work of the Editor. He expressed his appreciation of the aid and counsel he had received from President Piersol, and from other Officers of the College, including the General Chairman and the Committees of the Chicago Clinical Session.

Upon motion, seconded and regularly carried, the report of the Executive Secretary was received and placed on file.

PRESIDENT PIERSOL: "Members of the American College of Physicians, the time has come for me to turn over the gavel to worthier hands. Before I retire from the Chair, I cannot resist the opportunity of taking advantage of this chance to express to the entire membership the appreciation and gratitude I feel for their loyal support and coöperation during these trying times and throughout this past year.

"Without the generous response which was received from the members of this College, the present successful Clinical Session could not have been accomplished. I feel that it is due to the loyalty, enthusiasm and willingness of all of you as individuals, not alone your Officers, to coöperate in the efforts of this College that has made it possible to bring the organization through the past twelve months as successfully as it has been done.

"I turn over the office of President with a certain knowledge that next year will be much more successful than the past because I know so well the interest and the ability of the man who is to be my successor.

"It is therefore with a great deal of pleasure and pride in behalf of the College that I turn over this office to Dr. Jonathan C. Meakins, of Montreal, our present President."

PRESIDENT MEAKINS: "Masters and Fellows of the American College of Physicians: A little over a year ago I expressed my thanks very inadequately to you for electing me to this high office. I cannot, however, let this moment pass without expressing probably a selfish vice but that of pride at your apparent confidence in my capacity to carry on the high traditions of my predecessors.

"The College cannot stand still but must always advance to higher and firmer ground. It is a living force in our profession.

"Although the older Fellows have borne the burden of the day, it is to the younger Fellows that the future must be trusted. Therefore, it would be our duty to maintain for the College the high standards for admission of Associates and Fellows and also the excellence of the Clinical Sessions which now occupy a unique position in internal medicine. With the happy and unselfish coöperation of all your officers, there is no doubt that these objectives will be attained.

"I have a full appreciation of my responsibilities and wish to assure the Masters and Fellows of the College that I will do all in my power to justify their confidence in electing me to the exalted position of their President."

President Meakins then called for the report of the Nominating Committee, following which elections took place, as indicated below:

<i>President-Elect</i>	James Alex. Miller, New York, N. Y.
<i>First Vice President</i>	James H. Means, Boston, Mass.
<i>Second Vice President</i>	Randolph Lyons, New Orleans, La.
<i>Third Vice President</i>	James F. Churchill, San Diego, Calif.

Board of Regents

(Term expiring 1937)

George Morris Piersol, Philadelphia, Pa.
 William J. Kerr, San Francisco, Calif.
 Roger I. Lee, Boston, Mass.
 Sydney R. Miller, Baltimore, Md.
 G. Gill Richards, Salt Lake City, Utah

Board of Governors

(Term expiring 1937)

Fred W. Wilkerson	ALABAMA, Montgomery
W. Warner Watkins	ARIZONA, Phoenix
Lewis B. Flinn	DELAWARE, Wilmington
Turner Zeigler Cason	FLORIDA, Jacksonville
William R. Houston	GEORGIA, Augusta
James G. Carr	(Northern) ILLINOIS, Chicago
Ernest B. Bradley	KENTUCKY, Lexington
Edwin W. Gehring	MAINE, Portland
Henry M. Thomas, Jr.	MARYLAND, Baltimore
G. W. F. Rembert	MISSISSIPPI, Jackson
Louis H. Fligman	MONTANA, Helena
LeRoy S. Peters	NEW MEXICO, Albuquerque

Robert A. Cooke	(Eastern) NEW YORK, New York
A. B. Brower	OHIO, Dayton
T. Homer Coffen	OREGON, Portland
Charles T. Stone	TEXAS, Galveston
Rock Sleyster	WISCONSIN, Wauwatosa
Bailey K. Ashford	PUERTO RICO, San Juan
Fred Todd Cadham	MANITOBA, Winnipeg, Canada

(Term expiring 1936)

Robert B. Kerr	NEW HAMPSHIRE, Manchester
Clarence L. Andrews	NEW JERSEY, Atlantic City

(Term expiring 1935)

William B. Breed	MASSACHUSETTS, Boston
Louis E. Viko	UTAH, Salt Lake City

Ex Officio

Perceval S. Rossiter	UNITED STATES NAVY
----------------------------	--------------------

DR. JENNINGS: "Mr. President, I am sure the consensus of the members of the American College of Physicians is that the present Clinical Session is one of the best in the history of the College. I, therefore, move that a vote of sincere thanks be given to the General Chairman, Dr. James B. Herrick, to the various committees, and to the medical profession of Chicago for their cordial hospitality and the perfection of arrangements for the scientific sessions."

DR. COCKE: "It is with great satisfaction and real pleasure that I second Dr. Jennings' resolution."

The motion was carried unanimously by a rising vote.

PRESIDENT MEAKINS: "It is my pleasure to instruct our Executive Secretary to convey this resolution to our hosts here in Chicago."

There being no further business, upon motion regularly made, seconded and carried, the meeting adjourned at 5:35 o'clock.

Adjournment.

Attest: E. R. LOVELAND,
Executive Secretary

ANNALS OF INTERNAL MEDICINE

MAURICE C. PINCOFFS

Editor

VOLUME 7

(OLD SERIES, VOLUME XII)

1933-1934

Contents

NUMBER 1, JULY, 1933

Presentation of the John Phillips Memorial Prize to Dr. WILLIAM CASTLE	1
The Etiology of Pernicious Anemia and Related Macrocytic Anemias. W. B. CASTLE	2
Studies on the Function and Clinical Use of Cortin. FRANK A. HARTMAN	6
Differentiating Some Functions of the Anterior Pituitary Hormones. OSCAR RIDDLE	23
Effect of Hormones on Cellular Permeability. ERNST GELLHORN	33
Undernutrition and Its Treatment by Adequate Diet. J. M. STRANG and F. A. EVANS	45
Ultrahigh Frequency Pyretotherapy of Neurosyphilis. WALTER M. SIMP- SON, F. K. KISLIG, and E. C. SITTLER	64
The Clinical Significance of Gastric Acidity. Z. SAGAL, J. A. MARKS, and J. L. KANTOR	76
Coexistence of Pernicious Anemia and Lesions of the Gastrointestinal Tract. I. Carcinoma of the Stomach; Consideration of 20 Cases. H. M. CONNER and I. W. BIRKELAND	89
Renal Insufficiency Following Blood Transfusion—Recovery after Vene- section. H. T. VONDEESTEN and S. A. COSGROVE	105
Vitamin Therapy in Pulmonary Tuberculosis: IV. Comparison of the H-Ion Concentration of the Blood in Tuberculosis with Normals on the Same Dietary. P. D. CRIMM and H. L. WATSON	109
The Clinical Value of the Presumptive Kahn Test. T. CAJIGAS	114
The Source of Modern Medicine. SIR ANDREW MACPHAIL	120
Editorials	131
Reviews	134
College News Notes	140

NUMBER 2, AUGUST, 1933

Aspects of Carbohydrate and Fat Metabolism. C. H. BEST	145
The Analysis of High Caloric Diets in Relation to Weight Changes. J. M. STRANG and A. B. COX	152
The Rheumatic Lung. C. P. HOWARD	165
Treatment of Polycythemia. E. H. FALCONER	172
Polycythemia Associated with Pulmonary Disorders. J. J. WARING and W. B. YEGGE	190
A Standard Test for Measuring the Variability of Blood Pressure: Its Significance as an Index of the Prehypertensive State. E. A. HINES, JR. and GEORGE E. BROWN	209
The Diagnosis and Medical Treatment of Angina Pectoris. PAUL D. WHITE	218
Experimental and Clinical Studies in the Surgical Treatment of Angina Pectoris. JAMES C. WHITE	229
Management of Edema. CHARLES A. ELLIOTT	240

Problems of Pulmonary Tuberculosis in General Practice. REGINALD FITZ	245
A Graphic Study of the Changes in the Muscular Activity of the Stomach Associated with Certain Epigastric Symptoms. P. B. WELCH	251
The Relationship of the Autonomic Nervous System to General Medicine. T. P. SPRUNT	257
Editorials	266
Reviews	272
College News Notes	276

NUMBER 3, SEPTEMBER, 1933

The Internist as His Own Psychiatrist. ALFRED STENGEL	281
The Cerebral Circulation. XXV. Remarks on Clinical Physiology. STANLEY COBB	292
The Evidence for a Cerebral Vascular Mechanism in Epilepsy. WILDER PENFIELD	303
The Value of Alimentary Galactosuria in the Diagnosis of Jaundice. HENRY J. TUMEN and GEORGE MORRIS PIERSOL	311
Concerning Placental Hormones and Menstrual Disorders. A. D. CAMPBELL	330
The Effect of Vitamins and the Inorganic Elements on Growth and Resistance to Disease in Children. ALAN BROWN and FREDERICK F. TISDALL	342
Further Observations on the Treatment of Pernicious Anemia with Parenteral Horse Liver Extract; Including One Case of Pernicious Anemia Following Gastrectomy. OSCAR RICHTER, ARTHUR E. MEYER, and ANDREW C. IVY	353
Research in Electrocardiography. WILLIAM D. REID and SAMUEL H. CALDWELL	369
The Differential Diagnosis of Diseases of the Liver and Spleen with the Aid of Roentgenography after the Intravenous Injection of Thorium Dioxide Sol (Thorotrast): Experience with Eighty Patients. WALLACE M. YATER and LAURENCE S. OTELL	381
Some Aspects of Cell Physiology. W. J. V. OSTERHOUT	396
Editorials	401
Reviews	405
College News Notes	411

NUMBER 4, OCTOBER, 1933

Collapse Therapy of Bronchiectasis. E. RIST	417
Bilateral Splanchnic Nerve Section in a Juvenile Diabetic. GÉZA DE TAKATS and G. K. FENN	422
Chronic Arterial Occlusion of the Extremities. DUNCAN GRAHAM	431
The Diagnostic Use of Iodine in Thyrotoxicosis. J. H. MEANS	439
Schizophrenia from the Physiological Point of View. R. G. HOSKINS ..	445
Evaluation of Therapy in Chronic Atrophic Arthritis. W. PAUL HOLBROOK	457
The Indications for Collapse Therapy in Pulmonary Tuberculosis. I. D. BRONFIN	468
Calcareous Aortic Valvular Lesions. BURR M. HATHAWAY	484

The Treatment of Chronic Intractable Asthma with Pollen Extracts. GEORGE L. WALDBOTT	508
Renal Glycosuria. A. F. FOWLER	518
Editorials	530
Reviews	534
College News Notes	538

NUMBER 5, NOVEMBER, 1933

Hepatic Pathology in Exophthalmic Goiter. CARL V. WELLER	543
A Painless Histamine Skin Test: An Experimental Study. SAMUEL PERLOW	561
Intravenous Vaccine Therapy in Chronic Arthritis. WILLIAM B. RAWLS, B. J. GRUSKIN, and A. RESSA	566
Xanthoma Accompanied by Hypercholesterolemia, Occurring in an Other- wise Normal Individual and in an Individual with Acromegaly and Diabetes. THOMAS HODGE MCGAVACK and H. CLARE SHEPARDSON	582
Ultra-Violet Energy, Its Effect and Intensity at Various Locations and Altitudes. MELDRUM K. WYLDER, ROBERT S. ROCKWOOD, and SAM- UEL BUDD LIPPINCOTT	605
The Incidence of Hypertension Among Urban Japanese. HIROTOSHI HASHIMOTO, KEIJI AKATSUKA, ICHIRO TSUJII, and HAJIME SHIRAISHI	615
Gastrointestinal Allergy in Children. HORTON CASPARIS	625
Abscess of the Aorta; A Case with Perforation without Aneurysm. CHARLES W. MILLS and MAX PINNER	630
The Parenteral Administration of Magnesium Sulphate in Hypertension. BURTON L. ZOHMAN and BERNARD STERNBERG	643
Experimental and Clinical Studies of Ergotamine. V. The Action of Ergotamine on the Sympathetic Nervous System Stimulated by Epi- nephrine. Studies of the Metabolic Rate, Pulse Rate, Blood Pres- sure, Blood Sugar and the Total Leukocyte Count. JOHN B. YOU- MANS, CHARLES TRABUE, RALPH S. BUVINGER, and H. FRANK	653
Psychiatric Investigation in Internal Medicine. MARIE L. CARNS and ANNETTE C. WASHBURNE	664
Editorial	669
Reviews	677
College News Notes	682

NUMBER 6, DECEMBER, 1933

The Pathologic Anatomy of the Liver in Exophthalmic Goiter. DONALD C. BEAVER and JOHN DEJ. PEMBERTON	687
Bromide Psychoses: Diagnosis, Treatment and Prevention. MAX LEVIN	709
Subacute Bacterial Endocarditis. JOHN H. MUSSER	715
The Rôle of Desensitization in Recovery from Bacterial Infection. W. B. WHERRY	728
The Familial Incidence of Peptic Ulcer. HERMAN H. RIECKER	732
Toxicology and Assay of Methylene Blue. DAVID I. MACHT and WILTON C. HARDEN	738
Conservatism, the Keynote in the Treatment of Tuberculosis. C. H. COCKE	746

The Effect of Pilocarpine on the Volume, Free and Combined Acid, Total Chlorides and Pepsin of Gastric Secretion; and a Comparison with the Effects of Histamine Stimulation. LEO. J. MEIENBERG and CHARLES L. BROWN	762
The Incidence and Significance of the Sick Cell Trait. L. W. DIGGS, C. F. AHMANN, and JUANITA BIBB	769
Heart Block in the Young. I. I. LEMANN	779
Editorial	788
Reviews	791
College News Notes	795
Obituaries	797

NUMBER 7, JANUARY, 1934

Thromboangiitis Obliterans of Patients with Diabetes. BAYARD T. HORTON and FRANK N. ALLAN	799
Human Constitution. A Study of the Correlations between Physical Aspects of the Body and Susceptibility to Certain Diseases. WALTER FREEMAN	805
Paroxysmal Ventricular Tachycardia: An Etiological Study with Special Reference to the Type. CLAYTON J. LUNDY and LAWRENCE L. MCLELLAN	812
Fatal Tularemia. Review of Autopsied Cases with Report of a Fatal Case. LEWIS P. GUNDRY and C. GARDNER WARNER	837
Fragilitas Ossium in Five Generations. HENRY JOACHIM and MILTON G. WASCH	853
A Justification of the Diagnosis of Chronic Nervous Exhaustion. JOHN W. MACY and EDGAR V. ALLEN	861
Irradiation Treatment of Hyperthyroidism. GEORGE E. PFAHLER	868
The Cause of Death of Patients with Organic Heart Disease Subjected to Surgical Operation. W. K. PURKS	885
Myeloid Insufficiency. R. GOTTLIEB	895
The Importance of Bronchoscopy in Bronchiectasis. HORACE P. MARVIN	903
Editorial	913
Reviews	916
College News Notes	919
Obituaries	921
Abstract of Minutes of the Board of Regents	923

NUMBER 8, FEBRUARY, 1934

Rational Treatment of the Anemic Patient. WILLIAM P. MURPHY	939
Glycine in the Treatment of Myasthenia Gravis. EARL O. G. SCHMITT ...	948
The Pernicious Type of Nervous Dyspepsia. EDWARD C. KLEIN, JR. ...	960
Hepatic Complications in the Treatment of Syphilis; The Rose Bengal Test as a Means of Detecting Disturbances of Liver Function and Its Use as a Guide in the Therapy of Syphilis. GERSON R. BISKIND, NORMAN N. EPSTEIN, and WM. J. KERR	966
The Treatment of Circulatory Failure. LOUIS M. WARFIELD	981
Sporotrichosis; Report of a Case Originating in New York. GEORGE M. LEWIS and J. HOMER CUDMORE	991
The Relationship of Sex to Disease. EDGAR V. ALLEN	1000
Hypoglycemia and Hyperinsulinism. MILO K. TEDSTROM	1013

Pneumococcic Meningitis; Recovery with Felton's Serum. WILLIAM S. REVENO and NELSON McLAUGHLIN	1026
Chicago as a Medical Center	1033
Editorials	1048
Reviews	1052
College News Notes	1055
Obituaries	1057

NUMBER 9, MARCH, 1934

The Significance of the Hypertrophy and Hyperplasia of the Parathyroid Glands in Rickets and Osteomalacia. RUSSELL M. WILDER, GEORGE M. HIGGINS, and CHARLES SHEARD	1059
Chronic Pericardial Effusion in Myxedema. Report of a Case. E. B. FREEMAN	1070
The Effect of Calcium on the Storage of Colloid in the Thyroid Gland. JACOB KLEIN	1080
Nomenclature of the Disorders of Insulin Secretion: Diabetes Mellitus, Hyperinsulinism and Dysinsulinism. SEALE HARRIS	1084
Obliterating Thrombosis of the Pulmonary Arteries. W. M. FOWLER ..	1101
Parenteral Liver Therapy in Pernicious Anemia: Observations Covering Two Years of Continued Use. JOSEPH E. CONNERY and LEONARD J. GOLDWATER	1117
Mucin in the Treatment of Peptic Ulcer Associated with Renal and Hepatic Disease. ANDREW B. RIVERS and FRANCES R. VANZANT	1122
The Redundant Duodenum: Clinical Significance. THEODORE H. MORRISON and MAURICE FELDMAN	1126
The Hereditary and Familial Factor in Hypochromic Anemia with Achlorhydria. WILLIAM H. BARROW	1135
Tuberculoma of the Brain. MAURICE LEWISON, ELLIS B. FREILICH, and OSCAR B. RAGINS	1141
Editorials	1146
Reviews	1149
Program of the 18th Annual Clinical Session, Chicago	1153
College News Notes	1196
Obituaries	1198

NUMBER 10, APRIL, 1934

Splanchnic Nerve Section in Juvenile Diabetes. I. Selection of Cases for Operation. GÉZA DE TAKATS, G. K. FENN, and RUTH A. TRUMP ..	1201
A Consideration of the Gastric Ulcer-Cancer Problem, with the Report of a Case of Ulcerating Carcinoma in Which the Gastric Acidity Changed from Normal to Anacidity while under Observation. HARRY SHAY and EUGENE M. SCHLOSS	1218
Felty's Syndrome. Report of a Case with Complete Postmortem Findings. ALVIN E. PRICE and JOHN B. SCHOENFELD	1230
Tuberculoma of the Spinal Cord. F. L. JENNINGS	1240
The Value of a Neutralization Test of Gastric Acidity in Patients with Duodenal Ulcers and So-Called Pylorospasm. JEROME S. LEVY	1244
Acquired Heart Block with Adams-Stokes Attacks Dependent upon a Congenital Anomaly (Persistent Ostium Primum); Report of a Case with Detailed Histopathologic Study. WALLACE M. YATER, CHARLES W. BARRIER, and PAUL E. McNABB	1263

The Analgesic Effect of Hepatitis and Jaundice in Chronic Arthritis, Fibrositis and Sciatic Pain. PHILIP S. HENCH	1278
Calcification of the Pleura. JEROME HEAD	1295
"Allergic" Shock. III. From Substances Other Than Pollen and Serum. GEORGE L. WALDBOTT	1308
Report of Two Unusual Cases of Primary Carcinoma: I. Primary Carcinoma in the Liver, with Cirrhosis of the Liver, Occurring in a Female. II. Primary Carcinoma in the Jejunum. REUBEN FINKELSTEIN and MENDEL JACOBI	1319
Editorials	1327
Reviews	1331
College News Notes	1335
Obituaries	1338

NUMBER 11, MAY, 1934

Periarthritis Nodosa. A Brief Review of the Literature and a Report of One Case. ARTHUR C. CURTIS and ROBERT M. COFFEY	1345
Clinical Aspects of Pericardial Metastasis. BEN R. HENINGER	1359
Situs Inversus Viscerum Totalis in Siblings. Case Reports. EDWARD A. GALL and VICTOR F. WOOLF	1370
Report of a Case of Diverticulosis of the Small Intestine with a Critical Review of Recent Literature. JOHN CHAPMAN	1376
Electropylrexia; A Résumé of Therapeutic Applications and Technics. STAFFORD OSBORNE and D. E. MARKSON	1391
Hematological Response of Addisonian Pernicious Anemia to Brewer's Yeast. HOLLIS K. RUSSELL	1398
External Trauma in Relation to Ulcer of the Stomach and Duodenum. Report of Five Cases. IRVING GRAY	1403
Studies of Hypersensitiveness to the Emanations of the Caddis Fly (<i>Trichoptera</i>). V. A Report of Its Distribution. S. J. PARLATO, P. J. LADUCA, and O. C. DURHAM	1420
A Case of Persistent Lymphedema Involving the Left Arm, Left Face, and Left Thorax. RAMSDALL GURNEY and FRANKLYN HUBER	1431
<i>Sangre Impura</i> in Mora; A Study of Syphilis and Certain Other Diseases in the Population of Mora County, New Mexico. WALTER CLARKE	1436
Editorial	1456
Reviews	1458
College News Notes	1462

NUMBER 12, JUNE, 1934

Treatment of Angina Pectoris and Congestive Heart Failure by Total Ablation of the Thyroid in Patients without Thyrotoxicosis. X. With Particular Reference to the Pre- and Postoperative Medical Management. H. L. BLUMGART, D. D. BERLIN, DAVID DAVIS, J. E. F. RISEMAN and A. A. WEINSTEIN	1469
A Statistical Evaluation of Different Methods for the Detection of Arteriosclerosis in Diabetes Mellitus. I. M. RABINOWITCH, W. L. RITCHIE, and S. H. MCKEE	1478
Tularemia Pneumonia. P. G. BOMAN and A. J. BIANCO	1491
Developments and Disappointments in Blood Studies. ROGER I. LEE	1496
Multi-Plane Chest Electrocardiography. A Standardized Method of Chest Lead Applications. JOSEPH WEINSTEIN	1503

Malaria Therapy in Asymptomatic Neurosyphilis. PAUL A. O'LEARY ...	1513
Congenital Cystic Disease of the Lungs. Case Reports. LEWIS J. MOORMAN	1523
Mild Hypothyroidism. RALPH M. WATKINS	1534
The Use of Calcium Ortho-Iodoxybenzoate in the Treatment of Arthritis, with a Discussion of Its Possible Value in Some Other Orthopedic Conditions. THOMAS WHEELDON	1540
Dr. Richard Shuckburgh and Yankee Doodle. LOUIS H. RODDIS	1548
Editorial	1553
Reviews	1560
College News Notes	1562
Abridged Minutes of the Chicago Meeting	1565
Index	1585

ANNALS OF INTERNAL MEDICINE

AUTHOR INDEX

Volume 7, 1933-1934

- AHMANN, C. F., L. W. DIGGS—and J. BIBB. The Incidence and Significance of the Sick Cell Trait 769
- AKATSUKA, K., H. HASHIMOTO,—I. TSUJII and H. SHIRAIISHI. The Incidence of Hypertension among Urban Japanese 615
- ALLAN, F. N., B. T. HORTON and—. Thromboangiitis Obliterans of Patients with Diabetes 799
- ALLEN, E. V. The Relationship of Sex to Disease 1000
- , J. W. MACY and—. A Justification of the Diagnosis of Chronic Nervous Exhaustion 861
- APPLETON, J. L. T., JR. Bacterial Infection with Special Reference to Dental Practice. *Rev.* 918
- ARAFA, M. A. Modern Aspects of Gastro-Enterology. *Rev.* 409
- BALLENGER, E. G., B. LEWIS,—W. A. FRONTZ and H. G. HAMER. History of Urology. Volumes I and II. *Rev.* 792
- BARGEN, J. A., F. W. RANKIN,—and L. A. BUIE. The Colon, Rectum, and Anus. *Rev.* 917
- BARRIER, C. W., W. M. YATER,—and P. E. McNABB. Acquired Heart Block with Adams-Stokes Attacks Dependent upon a Congenital Anomaly (Persistent Ostium Primum). Report of a Case with Detailed Histopathologic Study 1263
- BARROW, W. H. The Hereditary and Familial Factor in Hypochromic Anemia with Achlorhydria 1135
- BASSETT, C. Mental Hygiene in the Community. *Rev.* 1150
- BEAVER, D. C. and J. DEJ. PEMBERTON. The Pathologic Anatomy of the Liver in Exophthalmic Goiter 687
- BERLIN, D. D., H. L. BLUMGART,—D. DAVIS, J. E. F. RISEMAN and A. A. WEINSTEIN. Treatment of Angina Pectoris and Congestive Heart Failure by Total Ablation of the Thyroid in Patients without Thyrotoxicosis. X. With Particular Reference to the Medical Management 1469
- BEST, C. H. Aspects of Carbohydrate and Fat Metabolism 145
- BEUTNER, R. Physical Chemistry of Living Tissues and Life Processes. *Rev.* 138
- BIANCO, A. J., P. G. BOMAN and—. Tularemic Pneumonia 1491
- BIBB, J., L. W. DIGGS, C. F. AHMANN and—. The Incidence and Significance of the Sick Cell Trait 769
- BIRKELAND, I. W., H. M. CONNER and—. Coexistence of Pernicious Anemia and Lesions of the Gastrointestinal Tract. I. Carcinoma of the Stomach; Consideration of Twenty Cases: Eleven Reported 89
- BISKIND, G. R., N. N. EPSTEIN and W. J. KERR. Hepatic Complications in the Treatment of Syphilis. The Rose Bengal Test as a Means of Detecting Disturbances of Liver Function and Its Use as a Guide in the Therapy of Syphilis 966
- BLOOMFIELD, A. L. and W. S. POLLAND. Gastric Acidity. Its Relation to Disease. *Rev.* 272
- BLUMER, G., Supervising Editor. T. S. MOISE, JR., Associate Editor. Practitioner's Library of Medicine and Surgery. Volume IV: Nontraumatic Surgery. *Rev.* 407
- , Volume V: Traumatic Surgery. T. S. MOISE, JR., Associate Editor. Volume VI: Obstetrics and Gynecology. L. K. MUSSELMAN, Associate Editor. *Rev.* 1458
- BLUMGART, H. L., D. D. BERLIN, D. DAVIS, J. E. F. RISEMAN and A. A. WEINSTEIN. Treatment of Angina Pectoris and Congestive Heart Failure by Total Ablation of the

Pre- and Postoperative Medical Management	1469	— and C. R. GILMOUR. Biochemistry of Medicine. <i>Rev.</i>	679
BOGERT, L. J. Diet and Personality. Fitting Food to Type and Environment. <i>Rev.</i>	1152	CAMPBELL, A. D. Concerning Placental Hormones and Menstrual Disorders .	330
BOMAN, P. G. and A. J. BIANCO. Tubercular Pneumonia	1491	CANTAROW, A. Calcium Metabolism and Calcium Therapy. <i>Rev.</i>	136
BRIDGES, M. A. and R. L. GALLUP. Dietetics for the Clinician. <i>Rev.</i>	535	CARNS, M. L. and A. C. WASHBURNE. Psychiatric Investigation in Internal Medicine	664
BRONFIN, I. D. The Indications for Collapse Therapy in Pulmonary Tuberculosis	468	CASPARIS, H. Gastrointestinal Allergy in Children	625
BROWN, A. and F. F. TISDALL. The Effect of Vitamins and the Inorganic Elements on Growth and Resistance to Disease in Children	342	CASTLE, W. B. The Etiology of Pernicious Anemia and Related Macrocytic Anemias	2
BROWN, C. L., L. J. MEIENBERG and—. The Effect of Pilocarpine on the Volume, Free and Combined Acid, Total Chlorides and Pepsin of Gastric Secretion; and a Comparison with the Effects of Histamine Stimulation	762	CHAPIN, H. D. and L. T. ROYSTER. Pediatrics. <i>Rev.</i>	679
BROWN, G. E., E. A. HINES, JR., and —. A Standard Test for Measuring the Variability of Blood Pressure: Its Significance as an Index of the Prehypertensive State	209	CHAPMAN, J. Report of a Case of Diverticulosis of the Small Intestine with a Critical Review of Recent Literature	1376
BUCKSTEIN, J. Peptic Ulcer. <i>Rev.</i> ..	137	CLARKE, W. <i>Sangre Impura</i> in Mora; a Study of Syphilis and Certain Other Diseases in the Population of Mora County, New Mexico	1436
BUIE, L. A., F. W. RANKIN, J. A. BARGEN and—. The Colon, Rectum, and Anus. <i>Rev.</i>	917	CLENDENING, L. Behind the Doctor. <i>Rev.</i>	1149
BUNZEL, B., L. I. DUBLIN and—. To Be or Not to Be. A Study of Suicide. <i>Rev.</i>	793	COBB, S. The Cerebral Circulation. XXV. Remarks on Clinical Physiology	292
BURROWS, H. Some Factors in the Localization of Disease in the Body. <i>Rev.</i>	536	COCKE, C. H. Conservatism, the Key-note in the Treatment of Tuberculosis	746
BUVINGER, R. S., J. B. YOUNG, C. TRABUE and—. Experimental and Clinical Studies of Ergotamine. V. The Action of Ergotamine on the Sympathetic Nervous System Stimulated by Epinephrine. Studies of the Metabolic Rate, Pulse Rate, Blood Pressure, Blood Sugar and Total Leukocyte Count	653	COFFEY, R. M., A. C. CURTIS and—. Periarthritis Nodosa. A Brief Review of the Literature and Report of One Case	1345
CAJIGAS, T. The Clinical Value of the Presumptive Kahn Test	114	CONNER, H. M. and I. W. BIRKELAND. Coexistence of Pernicious Anemia and Lesions of the Gastrointestinal Tract. I. Carcinoma of the Stomach; Consideration of Twenty Cases; Eleven Reported	89
CALDWELL, S. H., W. D. REID and—. Research in Electrocardiography ...	369	CONNERY, J. E. and L. J. GOLDWATER. Parenteral Liver Therapy in Pernicious Anemia: Observations Covering Two Years of Continued Use ..	1117
CAMERON, A. T. Recent Advances in Endocrinology. <i>Rev.</i>	1332	COSGROVE, S. A., H. T. VONDEESTEN and—. Renal Insufficiency Following Blood Transfusion—Recovery after Venesection	105
		COX, A. B., J. M. STRANG and—. The Analysis of High Caloric Diets in Relation to Weight Changes	152
		CRIMM, P. D. and H. L. WATSON.	

- Vitamin Therapy in Pulmonary Tuberculosis. IV. Comparison of the H-Ion Concentration of the Blood in Tuberculosis with Normals on the Same Dietary 109
- CUDMORE, J. H., G. M. LEWIS and—. Sporotrichosis; Report of a Case Originating in New York 991
- CURTIS, A. C. and R. M. COFFEY. Periarthritis Nodosa. A Brief Review of the Literature and Report of One Case 1345
- DAVIS, D., H. L. BLUMGART, D. D. BERLIN,—J. E. F. RISEMAN and A. A. WEINSTEIN. Treatment of Angina Pectoris and Congestive Heart Failure by Total Ablation of the Thyroid in Patients without Thyrotoxicosis. X. With Particular Reference to the Pre- and Postoperative Medical Management 1469
- DE TAKATS, G. and G. K. FENN. Bilateral Splanchnic Nerve Section in a Juvenile Diabetic 422
- , G. K. FENN and R. A. TRUMP. Splanchnic Nerve Section in Juvenile Diabetes. I. Selection of Cases for Operation 1201
- DICKINSON, R. L. Human Sex Anatomy 1560
- DIGGS, L. W., C. F. AHMANN and J. BIBB. The Incidence and Significance of the Sickle Cell Trait 769
- DOLL, E. H., W. M. PHELPS and R. T. MELCHER. Mental Deficiency Due to Birth Injuries. *Rev.* 794
- DUBLIN, L. I. and B. BUNZEL. To Be or Not to Be. A Study of Suicide. *Rev.* 793
- DURHAM, O. C., S. J. PARLATO, P. J. LADUCA and—. Studies of Hypersensitiveness to the Emanations of the Caddis Fly (*Trichoptera*). *V. Report of Its Distribution 1420
- ELLIOTT, C. A. Management of Edema 240
- ENGEL, E. W., M. I. SMITH,—and E. F. STOHLMAN. Further Studies on the Pharmacology of Certain Phenol Esters with Special Reference to the Relation of Chemical Constitution and Physiologic Action. The Histopathology of Some Neurotoxic Phenol Esters. *Rev.* 274
- ENGELBACH, W. Endocrine Medicine. Volume I: General Considerations. Volume II: The Infantile Endocrinopathies. Volume III: The Adolescent Endocrinopathies. The Adult Endocrinopathies. Volume IV: Bibliography, Index. *Rev.* 407
- EPSTEIN, N. N., G. R. BISKIND,—and W. J. KERR. Hepatic Complications in the Treatment of Syphilis. The Rose Bengal Test as a Means of Detecting Disturbances of Liver Function and Its Use as a Guide in the Therapy of Syphilis 966
- EVANS, F. A., J. M. STRANG and—. Undernutrition and Its Treatment by Adequate Diet 45
- FALCONER, E. H. Treatment of Polycythemia; the Reticulocyte Response to Venesection, Phenylhydrazin and Radiation 172
- FARLEY, D. L., O. H. P. PEPPER and—. Practical Hematological Diagnosis. *Rev.* 273
- FELDMAN, M., T. H. MORRISON and—. The Redundant Duodenum: Clinical Significance 1126
- FENN, G. K., G. DE TAKATS and—. Bilateral Splanchnic Nerve Section in a Juvenile Diabetic 422
- , G. DE TAKATS,—and R. A. TRUMP. Splanchnic Nerve Section in Juvenile Diabetes. I. Selection of Cases for Operation 1201
- FIFIELD, J. C. American and Canadian Hospitals. *Rev.* 275
- FINKELSTEIN, R. and M. JACOBI. Report of Two Unusual Cases of Primary Carcinoma: I. Primary Carcinoma in the Liver, with Cirrhosis of the Liver, Occurring in a Female. II. Primary Carcinoma in the Jejunum 1319
- FISCHER, M. H. and M. O. HOOKER. The Lyophilic Colloids (Their Theory and Practice). *Rev.* 1151
- FISCHL, V. and H. SCHLOSSBERGER. Handbook of Chemotherapy. Part I. Metal Free Organic Compounds. *Rev.* 1459
- FITZ, R. Problems of Pulmonary Tuberculosis in General Practice 245
- FLEMING, A. and G. F. PETRIE. Recent

- Advances in Vaccine and Serum Therapy. *Rev.* 1333
- FÖLDES, E. A New Approach to Dietetic Therapy. *Rev.* 535
- FOWLER, A. F. Renal Glycosuria 518
- FOWLER, W. M. Obliterating Thrombosis of the Pulmonary Arteries ... 1101
- FRANKLIN, E. J., Translator. De Venarum Ostiolis, 1603, of Hieronymus Fabricius of Aquapendente (1533?-1619). *Rev.* 1150
- FREEMAN, E. B. Chronic Pericardial Effusion in Myxedema: Report of Case 1070
- FREEMAN, W. Human Constitution: a Study of the Correlations between Physical Aspects of the Body and Susceptibility to Certain Diseases .. 805
- FREILICH, E. B., M. LEWISON,—and O. B. RAGINS. Tuberculoma of the Brain 1141
- FREUD, S. New Introductory Lectures on Psychoanalysis. *Rev.* 1052
- . The Interpretation of Dreams. *Rev.* 1052
- FRONTZ, W. A., B. LEWIS, E. G. BALLENGER,—and H. G. HAMER. History of Urology. Volumes I and II. *Rev.* 792
- GALL, E. A. and V. F. WOOLF. Situs Inversus Viscerum Totalis in Siblings. Case Reports 1370
- GALLUP, R. L., M. A. BRIDGES and—. Dietetics for the Clinician. *Rev.* .. 535
- GALT, W. Phyloanalysis: a Study in the Group of Phyletic Method of Behavior-Analysis. *Rev.* 1561
- GELLHORN, E. The Effect of Hormones on Cellular Permeability 33
- GERSHENFELD, L. Urine and Urinalysis. *Rev.* 534
- GERSTLE, M. The Doctor Discusses Your Questions. *Rev.* 1331
- GILMOUR, C. R., A. T. CAMERON and—. Biochemistry in Medicine. *Rev.* .. 679
- GLASSER, O. Wilhelm Conrad Röntgen and the Early History of the Roentgen-Rays. *Rev.* 1460
- GOLDWATER, L. J., J. E. CONNERY and—. Parenteral Liver Therapy in Pernicious Anemia: Observations Covering Two Years of Continued Use 1117
- GOTTLIEB, R. Myeloid Insufficiency .. 895
- GRAFE, E. Metabolic Diseases and Their Treatment. *Rev.* 1149
- GRAHAM, D. Chronic Arterial Occlusion of the Extremities 431
- GRAHAM, S. and N. MORRIS. Acidosis and Alkalosis. *Rev.* 408
- GRAY, I. External Trauma in Relation to Ulcer of the Stomach and Duodenum. Report of Five Cases 1403
- GRINKER, R. R. Neurology. *Rev.* 1458
- GRUSKIN, B. J., W. B. RAWLS,—and A. RESSA. Intravenous Vaccine Therapy in Chronic Arthritis 566
- GUNDRY, L. P. and C. G. WARNER. Fatal Tularemia; Review of Autopsied Cases with Report of a Fatal Case 837
- GURNEY, R. and F. HUBER. A Case of Persistent Lymphedema Involving the Left Arm, Left Face, and Left Thorax 1431
- GUTTMACHER, A. F. and E. RAND. Life in the Making. *Rev.* 791
- HAMER, H. G., B. LEWIS, E. G. BALLENGER, W. A. FRONTZ, and—. History of Urology. Volumes I and II. *Rev.* 792
- HARDEN, W. C., D. I. MACHT and—. Toxicology and Assay of Methylene Blue 738
- HARRIS, S. Nomenclature of the Disorders of Insulin Secretion: Diabetes Mellitus, Hyperinsulinism and Dysinsulinism. An Analytical Review of Data Relevant to the Classification and Terminology of the Secretory Disorders of the Islands of Langerhans of the Pancreas 1084
- HARTMAN, F. A. Studies on the Function and Clinical Use of Cortin 6
- HASHIMOTO, H., K. AKATSUKA, I. TSUJII and H. SHIRAIISHI. The Incidence of Hypertension among Urban Japanese 615
- HATHAWAY, B. M. Calcareous Aortic Valvular Lesions 484
- HEAD, J. Calcification of the Pleura . 1295
- HENCH, P. S. The Analgesic Effect of Hepatitis and Jaundice in Chronic Arthritis, Fibrositis and Sciatic Pain 1278
- HENINGER, B. R. Clinical Aspects of Pericardial Metastasis 1359
- HIGGINS, G. M., R. M. WILDER,—and

- C. SHEARD. The Significance of the Hypertrophy and Hyperplasia of the Parathyroid Glands in Rickets and Osteomalacia 1059
- HINES, E. A., JR. and G. E. BROWN. A Standard Test for Measuring the Variability of Blood Pressure: Its Significance as an Index of the Prehypertensive State. 209
- HOLBROOK, W. P. Evaluation of Therapy in Chronic Atrophic Arthritis .. 457
- HOOKE, M. O., M. H. FISCHER and —. The Lyophilic Colloids (Their Theory and Practice). *Rev.* 1151
- HORTON, B. T. and F. N. ALLAN. Thromboangiitis Obliterans of Patients with Diabetes 799
- HOSKINS, R. G. Schizophrenia from the Physiological Point of View 445
- . The Tides of Life. The Endocrine Glands in Bodily Adjustment. *Rev.* 406
- HOWARD, C. P. The Rheumatic Lung 165
- HUBER, F., R. GURNEY and —. A Case of Persistent Lymphedema Involving the Left Arm, Left Face, and Left Thorax 1431
- HUNT, T. C. The Common Causes of Chronic Indigestion. Differential Diagnosis and Treatment. *Rev.* 273
- HUTCHINSON, R., Editor. An Index of Treatment. *Rev.* 677
- IVY, A. C., O. RICHTER, A. E. MEYER and—. Further Observations on the Treatment of Pernicious Anemia with Parenteral Horse Liver Extract; Including One Case of Pernicious Anemia Following Gastrectomy 353
- JACOBI, M., R. FINKELSTEIN and—. Report of Two Unusual Cases of Primary Carcinoma: I. Primary Carcinoma in the Liver, with Cirrhosis of the Liver, Occurring in a Female. II. Primary Carcinoma in the Jejunum 1319
- JENNINGS, F. L. Tuberculoma of the Spinal Cord 1240
- JOACHIM, H. and M. G. WASCH. Fragilitas Ossium in Five Generations . 853
- KANTOR, J. L., Z. SAGAL, J. A. MARKS and—. The Clinical Significance of Gastric Acidity. A Study of 6679 Cases with Digestive Symptoms 76
- KARPMAN, B. Case Studies in the Psychopathology of Crime. *Rev.* 405
- KELLOGG, E. L. The Duodenum: Its Structure and Function, Its Diseases and Their Medical and Surgical Treatment. *Rev.* 137
- KERR, J. W. Osteitis Deformans. A Review of the Literature and Report of Eleven Cases. *Rev.* 791
- KERR, W. J., G. R. BISKIND, N. N. EPSTEIN and—. Hepatic Complications in the Treatment of Syphilis. The Rose Bengal Test as a Means of Detecting Disturbances of Liver Function and Its Use as a Guide in the Therapy of Syphilis 966
- KISLIG, F. K., W. M. SIMPSON,—and E. C. SITTLER. Ultrahigh Frequency Pyretotherapy of Neurosyphilis. A Preliminary Report 64
- KLEIN, E. C., JR. The Pernicious Type of Nervous Dyspepsia 960
- KLEIN, J. The Effect of Calcium on the Storage of Colloid in the Thyroid Gland 1080
- KOPP, M. E. Birth Control in Practice: Analysis of 10,000 Case Histories of the Birth Control Clinical Research Bureau. *Rev.* 1331
- KRUMBHAAR, E. B., Editor. Clio Medica: A Series of Primers on the History of Medicine. Volume X. Nutrition. G. LUSK. *Rev.* 916
- , Editor. Chinese Medicine. W. R. MORSE. *Rev.* 1460
- LADUCA, P. J., S. J. PARLATO,—and O. C. DURHAM. Studies of Hypersensitivity to the Emanations of the Caddis Fly (*Trichoptera*). V. Report of Its Distribution 1420
- LANE, L. L., C. V. VISCHER and—. A Handbook of Pulmonary Tuberculosis. *Rev.* 272
- LEE, R. I. Developments and Disappointments in Blood Studies 1496
- LEMANN, I. I. Heart Block in the Young 779
- LEVIN, M. Bromide Psychoses: Diagnosis, Treatment and Prevention ... 709
- LEVY, J. S. The Value of a Neutralization Test of Gastric Acidity in Pa-

- tients with Duodenal Ulcers and So-called Pylorospasm 1244
- LEWIS, B., E. G. BALLENGER, W. A. FRONTZ and H. G. HAMER. History of Urology. Volumes I and II. *Rev.* 792
- LEWIS, G. M. and J. H. CUDMORE. Sporotrichosis; Report of a Case Originating in New York 991
- LEWISON, M., E. B. FREILICH and O. B. RAGINS. Tuberculoma of the Brain 1141
- LIFSCHITZ, J. Der Dialektische Materialismus und die klinische Medizin. *Rev.* 680
- LIPPINCOTT, S. B., M. K. WYLDER, R. S. ROCKWOOD and—. Ultra-Violet Energy, Its Effect and Intensity at Various Locations and Altitudes ... 605
- LIPSCOMB, F. M. Diseases of Old Age. *Rev.* 1054
- LOONEY, W. W. Anatomy of the Brain and Spinal Cord. *Rev.* 406
- LUNDY, C. J. and L. L. McLELLAN. Paroxysmal Ventricular Tachycardia: an Etiological Study with Special Reference to the Type 812
- LUSK, G. Nutrition. Volume X in *Clio Medica: A Series of Primers on the History of Medicine*. E. B. KRUMBHAAR, Editor. *Rev.* 916
- MACARTNEY, W. N. Observations of a General Practitioner. *Rev.* 1333
- MACHT, D. I. and W. C. HARDEN. Toxicology and Assay of Methylene Blue 738
- MACPHAIL, SIR A. The Source of Modern Medicine. An Address to the American College of Physicians ... 120
- MACY, J. W. and E. V. ALLEN. A Justification of the Diagnosis of Chronic Nervous Exhaustion 861
- MARKS, J. A., Z. SAGAL,—and J. L. KANTOR. The Clinical Significance of Gastric Acidity. A Study of 6679 Cases with Digestive Symptoms 76
- MARKSON, D. E., S. OSBORNE and—. Electropyræxia; A Résumé of Therapeutic Applications and Technics ... 1391
- MARTIN, C. R. Hospital Medical Statistics. *Rev.* 1333
- MARVIN, H. P. The Importance of Bronchoscopy in Bronchiectasis 903
- McFARLAND, R. C. The Psychological Effects of Oxygen Deprivation (Anoxemia) on Human Behavior. *Rev.* 917
- McGAVACK, T. H. and H. C. SHEPARDSON. Xanthoma Accompanied by Hypercholesterolemia, Occurring in an otherwise Normal Individual, and in an Individual with Acromegaly and Diabetes 582
- McKEE, S. H., I. M. RABINOWITCH, W. L. RITCHIE and—. A Statistical Evaluation of Different Methods for the Detection of Arteriosclerosis in Diabetes Mellitus 1478
- McLAUGHLIN, N., W. S. REVENO and—. Pneumococcic Meningitis: Recovery with Felton's Serum 1026
- McLELLAN, L. L., C. J. LUNDY and—. Paroxysmal Ventricular Tachycardia: an Etiological Study with Special Reference to the Type 812
- McNABB, P. E., W. M. YATER, C. W. BARRIER and—. Acquired Heart Block with Adams-Stokes Attacks Dependent upon a Congenital Anomaly (Persistent Ostium Primum). Report of a Case with Detailed Histopathologic Study 1263
- MEAD, S. V. Diseases of the Mouth. *Rev.* 535
- MEANS, J. H. The Diagnostic Use of Iodine in Thyrotoxicosis 439
- MEIENBERG, L. J. and C. L. BROWN. The Effect of Pilocarpine on the Volume, Free and Combined Acid, Total Chlorides and Pepsin of Gastric Secretion; and a Comparison with the Effects of Histamine Stimulation 762
- MELCHER, R. T., E. H. DOLL, W. M. PHELPS and—. Mental Deficiency Due to Birth Injuries. *Rev.* 794
- MEYER, A. E., O. RICHTER,—and A. C. IVY. Further Observations on the Treatment of Pernicious Anemia with Parenteral Horse Liver Extract; Including One Case of Pernicious Anemia Following Gastrectomy 353
- MILLS, C. W. and M. PINNER. Abscess of the Aorta; a Case with Perforation without Aneurysm 630
- MOISE, T. S., JR., Associate Editor. G. BLUMER, Supervising Editor. Practitioner's Library of Medicine and

- Surgery. Volume IV: Nontraumatic Surgery. *Rev.* 407
- , Volume V: Traumatic Surgery. Volume VI: Obstetrics and Gynecology. L. K. MUSSELMAN, Associate Editor. *Rev.* 1458
- MOORE, J. E. The Modern Treatment of Syphilis. *Rev.* 1331
- MOORMAN, L. J. Congenital Cystic Disease of the Lungs. Case Reports .. 1523
- MORRIS, N., S. GRAHAM and—. Acidosis and Alkalosis. *Rev.* 408
- MORRISON, T. H. and M. FELDMAN. The Redundant Duodenum: Clinical Significance 1126
- MORSE, M. G. The Medical Secretary. *Rev.* 138
- MORSE, W. R. *Clio Medica*. Chinese Medicine. E. B. KRUMBHAAR, Editor. *Rev.* 1460
- MURPHY, W. P. Rational Treatment of the Anemic Patient 939
- MUSSELMAN, L. K., Associate Editor of The Practitioner's Library of Medicine and Surgery. Volume VI: Obstetrics and Gynecology. G. BLUMER, Supervising Editor. Volume V: Traumatic Surgery. T. S. MOÏSE, JR., Associate Editor. *Rev.* 1458
- MUSSER, J. H. Subacute Bacterial Endocarditis 715
- O'LEARY, P. A. Malaria Therapy in Asymptomatic Neurosyphilis 1513
- OSBORN, F., G. C. SCHWESINGER, and —. Heredity and Environment; Studies in the Genesis of Psychological Characteristics. *Rev.* 1560
- OSBORNE, S. and D. E. MARKSON. Electropyrexia; a Résumé of Therapeutic Application and Technics 1391
- OSTERHOUT, W. J. V. Some Aspects of Cell Physiology 396
- OTELL, L. S., W. M. YATER and—. The Differential Diagnosis of Diseases of the Liver and Spleen with the Aid of Roentgenography after the Intravenous Injection of Thorium Dioxide Sol (Thorotrast): Experience with Eighty Patients .. 381
- PARLATO, S. J., P. J. LADUCA and O. C. DURHAM. Studies of Hypersensitiveness to the Emanations of the Caddis Fly (*Trichoptera*). V. Report of Its Distribution 1420
- PEMBERTON, J. DEJ., D. C. BEAVER and —. The Pathologic Anatomy of the Liver in Exophthalmic Goiter 687
- PENFIELD, W. The Evidence for a Cerebral Vascular Mechanism in Epilepsy 303
- PEPPER, O. H. P. and D. L. FARLEY. Practical Hematological Diagnosis. *Rev.* 273
- PERLOW, S. A Painless Histamine Skin Test: An Experimental Study . 561
- PETRIE, G. F., A. FLEMING and—. Recent Advances in Vaccine and Serum Therapy. *Rev.* 1333
- PFAHLER, G. E. Irradiation Treatment of Hyperthyroidism 868
- PHELPS, W. M., E. H. DOLL, —and R. T. MELCHER. Mental Deficiency Due to Birth Injuries. *Rev.* 794
- PIERSOL, G. M., H. J. TUMEN and—. The Value of Alimentary Galactosuria in the Diagnosis of Jaundice .. 311
- PINNER, M., C. W. MILLS and—. Abscess of the Aorta; a Case with Perforation without Aneurysm 630
- POLLAND, W. S., A. L. BLOOMFIELD and —. Gastric Anacidity. Its Relation to Disease. *Rev.* 272
- POTTENGER, F. M. Presentation of the John Phillips Memorial Prize to Dr. William Castle 1
- PRICE, A. E. and J. B. SCHOENFELD. Felty's Syndrome. Report of a Case with Complete Postmortem Findings 1230
- PURKS, W. K. The Cause of Death of Patients with Organic Heart Disease Subjected to Surgical Operation 885
- RABINOWITCH, I. M. Diabetes Mellitus, a Handbook of Simplified Methods of Diagnosis and Treatment. *Rev.* 916
- , W. L. RITCHIE and S. H. McKEE. A Statistical Evaluation of Different Methods for the Detection of Arteriosclerosis in Diabetes Mellitus 1478
- RAGINS, O. B., M. LEWISON, E. B. FREILICH and—. Tuberculoma of the Brain 1141
- RAND, E., A. F. GUTTMACHER and—. Life in the Making. *Rev.* 791

- RANKIN, F. W., J. A. BARGEN and L. A. BUIE. The Colon, Rectum, and Anus. *Rev.* 917
- RAWLS, W. B., B. J. GRUSKIN and A. RESSA. Intravenous Vaccine Therapy in Chronic Arthritis 566
- REID, W. D. Diseases of the Heart. *Rev.* 272
- and S. H. CALDWELL. Research in Electrocardiography 369
- RESSA, A., W. B. RAWLS, B. J. GRUSKIN and—. Intravenous Vaccine Therapy in Chronic Arthritis 566
- REVENO, W. S. and N. McLAUGHLIN. Pneumococcic Meningitis: Recovery with Felton's Serum 1026
- RICHMOND, W. V. The Adolescent Boy. *Rev.* 793
- RICHTER, O., A. E. MEYER and A. C. IVY. Further Observations on the Treatment of Pernicious Anemia with Parenteral Horse Liver Extract; Including One Case of Pernicious Anemia Following Gastrectomy 353
- RIDDLE, O. Differentiating Some Functions of the Anterior Pituitary Hormones 23
- RIECKER, H. H. The Familial Incidence of Peptic Ulcer 732
- RISEMAN, J. E. F., H. L. BLUMGART, D. D. BERLIN, D. DAVIS,—and A. A. WEINSTEIN. Treatment of Angina Pectoris and Congestive Heart Failure by Total Ablation of the Thyroid in Patients without Thyrotoxicosis. X. With Particular Reference to the Pre- and Postoperative Medical Management 1469
- RIST, E. Collapse Therapy of Bronchiectasis 417
- RITCHIE, W. L., I. M. RABINOWITCH, —and S. H. McKEE. A Statistical Evaluation of Different Methods for the Detection of Arteriosclerosis in Diabetes Mellitus 1478
- RIVERS, A. B. and F. R. VANZANT. Mucin in the Treatment of Peptic Ulcer Associated with Renal and Hepatic Disease 1122
- ROCKWOOD, R. S., M. K. WYLDER,—and S. B. LIPPINCOTT. Ultra-Violet Energy, Its Effect and Intensity at Various Locations and Altitudes 605
- RODDIS, L. H. Dr. Richard Shuckburgh and Yankee Doodle 1548
- ROYSTER, L. T., H. D. CHAPIN and—. Pediatrics. *Rev.* 679
- RUSSELL, H. K. Hematological Response of Addisonian Pernicious Anemia to Brewer's Yeast 1398
- SAGAL, Z., J. A. MARKS and J. L. KANTOR. The Clinical Significance of Gastric Acidity. A Study of 6679 Cases with Digestive Symptoms 76
- SAVILL, T. D. A System of Clinical Medicine. *Rev.* 1461
- SCHLOSS, E. M., H. SHAY and—. A Consideration of the Gastric Ulcer-Cancer Problem, with the Report of a Case of Ulcerating Carcinoma in Which the Gastric Acidity Changed from Normal to Anacidity while under Observation 1218
- SCHLOSSBERGER, H., V. FISCHL and—. Handbook of Chemotherapy. Part I. Metal Free Organic Compounds. *Rev.* 1459
- SCHMITT, E. O. G. The Use of Glycine in the Treatment of Myasthenia Gravis 948
- SCHOENFELD, J. B., A. E. PRICE and—. Felty's Syndrome. Report of a Case with Complete Postmortem Findings 1230
- SCHWESINGER, G. C. and F. OSBORN. Heredity and Environment; Studies in the Genesis of Psychological Characteristics. *Rev.* 1560
- SHAY, H. and E. M. SCHLOSS. A Consideration of the Gastric Ulcer-Cancer Problem, with the Report of a Case of Ulcerating Carcinoma in Which the Gastric Acidity Changed from Normal to Anacidity while under Observation 1218
- SHEARD, C., R. M. WILDER, G. M. HIGGINS and—. The Significance of the Hypertrophy and Hyperplasia of the Parathyroid Glands in Rickets and Osteomalacia 1059
- SHEPARDSON, H. C., T. H. McGAVACK and—. Xanthoma Accompanied by Hypercholesterolemia, Occurring in an otherwise Normal Individual, and in an Individual with Acromegaly and Diabetes 582

- SHIRAISHI, H., H. HASHIMOTO, K. AKATSUKA, I. TSUJII and—. The Incidence of Hypertension among Urban Japanese 615
- SHORT, A. R., Editor. An Index of Prognosis and End-Results of Treatment. *Rev.* 678
- SIGERIST, H. E. The Great Doctors. *Rev.* 1149
- SIMPSON, W. M., F. K. KISLIG and E. C. SITTLER. Ultrahigh Frequency Pyretotherapy of Neurosyphilis. A Preliminary Report 64
- SITTLER, E. C., W. M. SIMPSON, F. K. KISLIG and—. Ultrahigh Frequency Pyretotherapy of Neurosyphilis. A Preliminary Report 64
- SMITH, M. I., E. W. ENGEL and E. F. STOHLMAN. Further Studies on the Pharmacology of Certain Phenol Esters with Special Reference to the Relation of Chemical Constitution and Physiologic Action. The Histopathology of Some Neurotoxic Phenol Esters. *Rev.* 274
- SPRUNT, T. P. The Relationship of the Autonomic Nervous System to General Medicine 257
- STENGEL, A. The Internist as His Own Psychiatrist 281
- STEPHEN, K. Psychoanalysis and Medicine. A Study of the Wish to Fall Ill. *Rev.* 792
- STERN, N. S. Clinical Diagnosis: Physical and Differential. *Rev.* 136
- STERNBERG, B., B. L. ZOHMAN and—. The Parenteral Administration of Magnesium Sulphate in Hypertension 643
- STOHLMAN, E. F., M. I. SMITH, E. W. ENGEL and—. Further Studies on the Pharmacology of Certain Phenol Esters with Special Reference to the Relation of Chemical Constitution and Physiologic Action. The Histopathology of Some Neurotoxic Phenol Esters. *Rev.* 274
- STRANG, J. M. and A. B. COX. The Analysis of High Caloric Diets in Relation to Weight Changes 152
- and F. A. EVANS. Undernutrition and Its Treatment by Adequate Diet 45
- SWANBERG, H. Radiologic Maxims. *Rev.* 1052
- TEDSTROM, M. K. Hypoglycemia and Hyperinsulinism 1013
- TISDALL, F. F., A. BROWN and—. The Effect of Vitamins and the Inorganic Elements on Growth and Resistance to Disease in Children 342
- TRABUE, C., J. B. YOUNG, and R. S. BUVINGER. Experimental and Clinical Studies of Ergotamine. V. The Action of Ergotamine on the Sympathetic Nervous System Stimulated by Epinephrine. Studies of the Metabolic Rate, Pulse Rate, Blood Pressure, Blood Sugar and Total Leukocyte Count 653
- TRUMP, R. A., G. DE TAKATS, G. K. FENN and—. Splanchnic Nerve Section in Juvenile Diabetes. I. Selection of Cases for Operation 1201
- TSUJII, I., H. HASHIMOTO, K. AKATSUKA, and H. SHIRAISHI. The Incidence of Hypertension among Urban Japanese 615
- TUMEN, H. J. and G. M. PIERSOL. The Value of Alimentary Galactosuria in the Diagnosis of Jaundice 311
- ULLMANN, E. V. Diet in Sinus Infections and Colds. *Rev.* 680
- VANZANT, F. R., A. B. RIVERS and—. Mucin in the Treatment of Peptic Ulcer Associated with Renal and Hepatic Disease 1122
- VISCHER, C. W. and L. L. LANE. A Handbook of Pulmonary Tuberculosis. *Rev.* 272
- VONDEESTEN, H. T. and S. A. COSGROVE. Renal Insufficiency Following Blood Transfusion—Recovery after Venesection 105
- VONDERLEHR, R. A. Malaria Treatment of Parenchymatous Syphilis of the Central Nervous System. *Rev.* 1052
- VON FEUCHTERSLEBEN, BARON E. Hygiene of the Mind. *Rev.* 1053
- WALDBOTT, G. L. "Allergic Shock." III. From Substances other than Pollen and Serum 1308
- The Treatment of Chronic Intractable Asthma with Pollen Extracts 508

- WARFIELD, L. M. The Treatment of Circulatory Failure 981
- WARING, J. J. and W. B. YEGGE. Polycythemia in Association with Pulmonary Disorders 190
- WARNER, C. G., L. P. GUNDRY and—. Fatal Tularemia; Review of Autopsied Cases with Report of a Fatal Case 837
- WASCH, M. G., H. JOACHIM and—. Fragilitas Ossium in Five Generations 853
- WASHBURN, A. C., M. L. CARNS and—. Psychiatric Investigation in Internal Medicine 664
- WATKINS, R. M. Mild Hypothyroidism 1534
- WATSON, H. L., P. D. CRIMM and—. Vitamin Therapy in Pulmonary Tuberculosis. IV. Comparison of the H-Ion Concentration of the Blood in Tuberculosis with Normals on the Same Dietary 109
- WEINSTEIN, A. A., H. L. BLUMGART, D. D. BERLIN, D. DAVIS, J. E. F. RISEMAN and—. Treatment of Angina Pectoris and Congestive Heart Failure by Total Ablation of the Thyroid in Patients without Thyrotoxicosis. X. With Particular Reference to the Pre- and Postoperative Medical Management 1469
- WEINSTEIN, J. Multi-Plane Chest Electrocardiography. A Standardized Method of Chest Lead Applications 1503
- WELCH, P. B. A Graphic Study of the Changes in the Muscular Activity of the Stomach Associated with Certain Epigastric Symptoms 251
- WELLER, C. V. Hepatic Pathology in Exophthalmic Goiter 543
- WHEELDON, T. The Use of Calcium Ortho-Iodoxybenzoate in the Treatment of Arthritis, with a Discussion of Its Possible Value in Some Other Orthopedic Conditions 1540
- WHERRY, W. B. The Role of Desensitization in Recovery from Bacterial Infection 728
- WHITE, J. C. Experimental and Clinical Studies in the Surgical Treatment of Angina Pectoris 229
- WHITE, P. D. The Diagnosis and Medical Treatment of Angina Pectoris 218
- WILDER, R. M., G. M. HIGGINS and C. SHEARD. The Significance of the Hypertrophy and Hyperplasia of the Parathyroid Glands in Rickets and Osteomalacia 1059
- WILLIAMS, F. E. Adolescence: Studies in Mental Hygiene. *Rev.* 793
- WOLFE, W. B. Nervous Breakdown. *Rev.* 534
- WOOLF, V. F., E. A. GALL and—. Situs Inversus Viscerum Totalis in Siblings. Case Reports 1370
- WYLDER, M. K., R. S. ROCKWOOD and S. B. LIPPINCOTT. Ultra-Violet Energy, Its Effect and Intensity at Various Locations and Altitudes 605
- YATER, W. M., C. W. BARRIER and P. E. McNABB. Acquired Heart Block with Adams-Stokes Attacks Dependent upon a Congenital Anomaly (Persistent Ostium Primum). Report of a Case with Detailed Histopathologic Study 1263
- and L. S. OTELL. The Differential Diagnosis of Diseases of the Liver and Spleen with the Aid of Roentgenography after the Intravenous Injection of Thorium Dioxide Sol (Thorotrast): Experience with Eighty Patients 381
- YEGGE, W. B., J. J. WARING and—. Polycythemia in Association with Pulmonary Disorders 190
- YOUNG, J. B., C. TRABUE and R. S. BUVINGER. Experimental and Clinical Studies of Ergotamine. V. The Action of Ergotamine on the Sympathetic Nervous System Stimulated by Epinephrine. Studies of the Metabolic Rate, Pulse Rate, Blood Pressure, Blood Sugar and the Total Leukocyte Count 653
- ZOHMAN, B. L. and B. STERNBERG. The Parenteral Administration of Magnesium Sulphate in Hypertension 643

ANNALS OF INTERNAL MEDICINE

SUBJECT INDEX

Volume 7, 1933-1934

- A**BSCESS of the Aorta; a Case with Perforation without Aneurysm. C. W. MILLS and M. PINNER 630
- Acidosis and Alkalosis. S. GRAHAM and N. MORRIS. *Rev.* 408
- Acquired Heart Block with Adams-Stokes Attacks Dependent upon a Congenital Anomaly (Persistent Ostium Primum); Report of a Case with Detailed Histopathologic Study. W. M. YATER, C. W. BARRIER and P. E. McNABB 1263
- Acromegaly and Diabetes, Xanthoma Accompanied by Hypercholesterolemia, Occurring in an Otherwise Normal Individual, and in an Individual with—. T. H. McGAVACK and H. C. SHEPARDSON 582
- Adolescence: Studies in Mental Hygiene. F. E. WILLIAMS. *Rev.* 793
- Adolescent Boy, The—. W. V. RICHMOND. *Rev.* 793
- Adrenal Cortex, The Influence of the—upon Salt and Water Metabolism. *Edit.* 402
- Air Traffic and Disease. *Edit.* 1329
- Alkalosis, Acidosis and—. S. GRAHAM and N. MORRIS. *Rev.* 408
- "Allergic Shock." III. From Substances other than Pollen and Serum. G. L. WALDBOTT 1308
- Allergy in Children, Gastrointestinal—. H. CASPARIS 625
- Amebiasis. *Edit.* 788
- American and Canadian Hospitals. J. C. FIFIELD. *Rev.* 275
- Anacidity, Gastric—. Its Relation to Disease. A. L. BLOOMFIELD and W. S. POLLAND. *Rev.* 272
- Analgesic Effect of Hepatitis and Jaundice in Chronic Arthritis, Fibrositis and Sciatic Pain, The—. P. S. HENCH 1278
- Analysis of High Caloric Diets in Relation to Weight Changes, The—. J. M. STRANG and A. B. COX 152
- Anatomy, Human Sex—. R. L. DICKINSON. *Rev.* 1560
- Anatomy of the Brain and Spinal Cord. W. W. LOONEY. *Rev.* 406
- Anemia. Rational Treatment of the Anemic Patient. W. P. MURPHY .. 939
- Anemia with Achlorhydria, The Hereditary and Familial Factor in Hypochromic—. W. H. BARROW 1135
- Anemic Patient, Rational Treatment of the—. W. P. MURPHY 939
- Angina Pectoris, Experimental and Clinical Studies in the Surgical Treatment of—. J. C. WHITE 229
- Angina Pectoris, The Diagnosis and Medical Treatment of—. P. D. WHITE 218
- Angina Pectoris, Treatment of—and Congestive Heart Failure by Total Ablation of the Thyroid in Patients without Thyrotoxicosis. X. With Particular Reference to the Pre- and Postoperative Medical Management. H. L. BLUMGART, D. D. BERLIN, D. DAVIS, J. E. F. RISEMAN and A. A. WEINSTEIN 1469
- Anleitung zur frühzeitigen Erkennung der Krebskrankheit. *Rev.* 536
- Anus, The Colon, Rectum, and—. F. W. RANKIN, J. A. BARGEN and L. A. BUIE. *Rev.* 917
- Aorta, Abscess of the—; A Case with Perforation without Aneurysm. C. W. MILLS and M. PINNER 630
- Aortic Valvular Lesions, Calcareous—. B. M. HATHAWAY 484
- Aortitis, Syphilitic—. *Edit.* 133
- Arterial Occlusion of the Extremities, Chronic—. D. GRAHAM 431
- Arteries. Chronic Arterial Occlusion of the Extremities. D. GRAHAM .. 431
- Arteries, Obliterating Thrombosis of the Pulmonary—. W. M. FOWLER.. 1101
- Arteriosclerosis in Diabetes Mellitus, A Statistical Evaluation of Different Methods for the Detection of—. I. M. RABINOWITCH, W. L. RITCHIE and S. H. McKEE 1478
- Arthritis, Evaluation of Therapy in

- Chronic Atrophic—. W. P. HOLBROOK 457
- Arthritis, Intravenous Vaccine Therapy in Chronic—. W. B. RAWLS, B. J. GRUSKIN and A. RESSA 566
- Arthritis, The Analgesic Effect of Hepatitis and Jaundice in Chronic—, Fibrositis and Sciatic Pain. P. S. HENCH 1278
- Arthritis, The Use of Calcium Ortho-Iodoxybenzoate in the Treatment of —, with a Discussion of Its Possible Value in Some Other Orthopedic Conditions. T. WHEELDON 1540
- Aspects of Carbohydrate and Fat Metabolism. C. H. BEST 145
- Asthma, The Treatment of Chronic Intractable—with Pollen Extracts. G. L. WALDBOTT 508
- Autonomic Nervous System, The Relationship of the—to General Medicine. T. P. SPRUNT 257
- B**ACTERIAL Infection with Special Reference to Dental Practice. J. L. T. APPLETON, JR. *Rev.* 918
- Behind the Doctor. L. CLENDENING. *Rev.* 1149
- Bilateral Splanchnic Nerve Section in a Juvenile Diabetic. G. DE TAKATS and G. K. FENN 422
- Biochemistry of Medicine. A. T. CAMERON and C. R. GILMOUR. *Rev.* 679
- Birth Control in Practice: Analysis of 10,000 Case Histories of the Birth Control Clinical Research Bureau. M. E. KOPP. *Rev.* 1331
- Birth Injuries, Mental Deficiency Due to—. E. H. DOLL, W. M. PHELPS and R. T. MELCHER. *Rev.* 794
- Blood Pressure, A Standard Test for Measuring the Variability of—: Its Significance as an Index of the Prehypertensive State. E. A. HINES, JR. and G. E. BROWN 209
- Blood Studies, Developments and Disappointments in—. R. I. LEE 1496
- Blood Transfusion, Renal Insufficiency Following—; Recovery after Venesection. H. T. VONDEESTEN and S. A. COSGROVE 105
- Blood Vessels, The Effect of Tobacco on Diseases of the—. *Edit.* 1456
- Brain and Spinal Cord, Anatomy of the—. W. W. LOONEY. *Rev.* 406
- Bromide Psychoses: Diagnosis, Treatment and Prevention. M. LEVIN .. 709
- Bronchiectasis, Collapse Therapy of—. E. RIST 417
- Bronchiectasis, The Importance of Bronchoscopy in—. H. P. MARVIN .. 903
- Bronchoscopy, The Importance of—in Bronchiectasis. H. P. MARVIN 903
- C**ADDIS Fly (*Trichoptera*), Studies of Hypersensitiveness to the Emanations of the—. V. A Report of Its Distribution. S. J. PARLATO, P. J. LADUCA and O. C. DURHAM 1420
- Calcareous Aortic Valvular Lesions. B. M. HATHAWAY 484
- Calcium, The Effect of—on the Storage of Colloid in the Thyroid Gland. J. KLEIN 1080
- Calcium Metabolism and Calcium Therapy. A. CANTAROW. *Rev.* 136
- Calcium Ortho-Iodoxybenzoate in the Treatment of Arthritis, The Use of —, with a Discussion of Its Possible Value in Some Other Orthopedic Conditions. T. WHEELDON 1540
- Cancer. Anleitung zur frühzeitigen Erkennung der Krebskrankheit. *Rev.* 536
- Carbohydrate and Fat Metabolism, Aspects of—. C. H. BEST 145
- Carcinoma, Report of Two Unusual Cases of Primary—: I. Primary Carcinoma in the Liver, with Cirrhosis of the Liver, Occurring in a Female. II. Primary Carcinoma in the Jejunum. R. FINKELSTEIN and M. JACOBI 1319
- Carcinoma of the Stomach. Coexistence of Pernicious Anemia and Lesions of the Gastrointestinal Tract. I.—. Consideration of Twenty Cases: Eleven Reported. H. M. CONNER and I. W. BIRKELAND 89
- Case of Persistent Lymphedema Involving the Left Arm, Left Face, and Left Thorax, A—. R. GURNEY and F. HUBER 1431
- Case Studies in the Psychopathology of Crime. B. KARPMAN. *Rev.* 405
- Cause of Death of Patients with Organic Heart Disease Subjected to Surgical Operation, The—. W. K. PURKS 885
- Causes of Chronic Indigestion, The

- Common—. Differential Diagnosis and Treatment. T. C. HUNT. *Rev.* 273
- Cell Physiology, Some Aspects of—. W. J. V. OSTERHOUT 396
- Cerebral Circulation, The—. XXV. Remarks on Clinical Physiology. S. COBB 292
- Cerebral Vascular Mechanism, The Evidence for a—in Epilepsy. W. PENFIELD 303
- Chemistry, Physical—of Living Tissues and Life Processes. R. BEUTNER. *Rev.* 138
- Chemotherapy, Handbook of—. Part I. Metal Free Organic Compounds. V. FISCHL and H. SCHLOSSBERGER. *Rev.* 1459
- Chicago as a Medical Center 1033
- Chronic Arterial Occlusion of the Extremities. D. GRAHAM. 431
- Chronic Pericardial Effusion in Myxedema: Report of Case. E. B. FREEMAN. 1070
- Circulatory Failure, The Treatment of—. L. M. WARFIELD 981
- Cirrhosis of the Liver, Primary Carcinoma in the Liver, with—Occurring in a Female. II. Primary Carcinoma in the Jejunum. Report of Two Unusual Cases of Primary Carcinoma: I—. R. FINKELSTEIN and M. JACOBI 1319
- Clinical Aspects of Pericardial Metastasis. B. R. HENINGER. 1359
- Clinical Significance of Gastric Acidity, The—. A Study of 6679 Cases with Digestive Symptoms. Z. SAGAL, J. A. MARKS and J. L. KANTOR 76
- Clinical Value of the Presumptive Kahn Test, The—. T. CAJIGAS 114
- Clio Medica: A Series of Primers on the History of Medicine. E. B. KRUMBHAAR, Editor. Volume X. Nutrition. G. LUSK. *Rev.* 916
- Clio Medica. Chinese Medicine. W. R. MORSE. E. B. KRUMBHAAR, Editor. *Rev.* 1460
- Coexistence of Pernicious Anemia and Lesions of the Gastrointestinal Tract. I. Carcinoma of the Stomach. Consideration of Twenty Cases: Eleven Reported. H. M. CONNER and I. W. BIRKELAND 89
- Colds, Diet in Sinus Infections and—. E. V. ULLMANN. *Rev.* 680
- Collapse Therapy of Bronchiectasis. E. RIST 417
- Colloids, The Lyophilic—(Their Theory and Practice). M. H. FISCHER and M. O. HOOKER. *Rev.* 1151
- Colon, Rectum, and Anus, The—. F. W. RANKIN, J. A. BARGEN and L. A. BUIE. *Rev.* 917
- Concerning Placental Hormones and Menstrual Disorders. A. D. CAMPBELL 330
- Congenital Anomaly (Persistent Ostium Primum), Acquired Heart Block with Adams-Stokes Attacks Dependent upon a—; Report of a Case with Detailed Histopathologic Study. W. M. YATER, C. W. BARRIER and P. E. McNABB 1263
- Congenital Cystic Disease of the Lungs. Case Reports. L. J. MOORMAN 1523
- Conservatism, the Keynote in the Treatment of Tuberculosis. C. H. COCKE 746
- Consideration of the Gastric Ulcer-Cancer Problem, A—; with the Report of a Case of Ulcerating Carcinoma in Which the Gastric Acidity Changed from Normal to Anacidity while under Observation. H. SHAY and E. M. SCHLOSS 1218
- Constitution, Human—: A Study of the Correlations between Physical Aspects of the Body and Susceptibility to Certain Diseases. W. FREEMAN. 805
- Coronary Sclerosis. *Edit.* 913
- Cortin, Studies on the Function and Clinical Use of—. F. A. HARTMAN 6
- D**E Venarum Ostiolis, 1603, of Hieronymus Fabricius of Aquapendente (1533?-1619). Translated by E. J. FRANKLIN. *Rev.* 1150
- Dental Practice, Bacterial Infection with Special Reference to—. J. L. T. APPLETON, JR. *Rev.* 918
- Desensitization, The Role of—in Recovery from Bacterial Infection. W. B. WHERRY 728
- Developments and Disappointments in Blood Studies. R. I. LEE 1496
- Diabetes. Bilateral Splanchnic Nerve Section in a Juvenile Diabetic. G. DE TAKATS and G. K. FENN 422
- Diabetes, Splanchnic Nerve Section in Juvenile—. I. Selection of Cases for

- Operation. G. DE TAKATS, G. K. FENN and R. A. TRUMP 1201
- Diabetes, Thromboangiitis Obliterans of Patients with—. B. T. HORTON and F. N. ALLAN 799
- Diabetes, Xanthoma Accompanied by Hypercholesterolemia, Occurring in an Otherwise Normal Individual, and in an Individual with Acromegaly and—. T. H. MCGAVACK and H. C. SHEPARDSON 582
- Diabetes Mellitus, a Handbook of Simplified Methods of Diagnosis and Treatment. I. M. RABINOWITCH. *Rev.* 916
- Diabetes Mellitus, a Statistical Evaluation of Different Methods for the Detection of Arteriosclerosis in—. I. M. RABINOWITCH, W. L. RITCHIE and S. H. MCKEE 1478
- Diabetes Mellitus, Hyperinsulinism and Dysinsulinism; An Analytical Review of Data Relevant to the Classification and Terminology of the Secretory Disorders of the Islands of Langerhans of the Pancreas. Nomenclature of the Disorders of Insulin Secretion;—. S. HARRIS 1084
- Diabetic, Bilateral Splanchnic Nerve Section in a Juvenile—. G. DE TAKATS and G. K. FENN 422
- Diagnosis, Clinical—: Physical and Differential. N. S. STERN. *Rev.* .. 136
- Diagnosis and Medical Treatment of Angina Pectoris, The—. P. D. WHITE 218
- Diagnostic Use of Iodine in Thyrotoxicosis, The—. J. H. MEANS 439
- Dialektische Materialismus und die klinische Medizin, Der—. J. LIFSCHITZ. *Rev.* 680
- Diet, Undernutrition and Its Treatment by Adequate—. J. M. STRANG and F. A. EVANS 45
- Diet and Personality. Fitting Food to Type and Environment. L. J. BOGERT. *Rev.* 1152
- Diet in Sinus Infections and Colds. E. V. ULLMANN. *Rev.* 680
- Dietetic Therapy, A New Approach to—. E. FÖLDES. *Rev.* 535
- Dietetics for the Clinician. M. A. BRIDGES and R. L. GALLUP. *Rev.* .. 535
- Diets in Relation to Weight Changes, The Analysis of High Caloric—. J. M. STRANG and A. B. COX 152
- Differential Diagnosis of Diseases of the Liver and Spleen with the Aid of Roentgenography after the Intravenous Injection of Thorium Dioxide Sol (Thorotrast), The—: Experience with Eighty Patients. W. M. YATER and L. S. OTELL 381
- Differentiating Some Functions of the Anterior Pituitary Hormones. O. RIDDLE 23
- Dinitrophenol. J. M. Non Nocere. *Edit.* 1327
- Disease, Air Traffic Valv—. *Edit.* 1329
- Disease, The Relationship of Sex to—. E. V. ALLEN 1000
- Disease in the Body, Some Factors in the Localization of—. H. BURROWS. *Rev.* 536
- Diseases of Old Age. F. M. LIPSCOMB. *Rev.* 1054
- Diseases of the Heart. W. D. REID. *Rev.* 272
- Diseases of the Mouth. S. V. MEAD. *Rev.* 535
- Diverticulosis of the Small Intestine, Report of a Case of—with a Critical Review of Recent Literature. J. CHAPMAN 1376
- Doctor Discusses Your Questions, The—. M. GERSTLE. *Rev.* 1331
- Doctors, The Great—. H. E. SIGERIST. *Rev.* 114
- Dreams, The Interpretation of—. S. FREUD. *Rev.* 1052
- Drug Bill, The New Pure Food and—. *Edit.* 1048
- Duodenal Ulcers, The Value of a Neutralization Test of Gastric Acidity in Patients with—and So-Called Pylorospasm. J. S. LEVY 1244
- Duodenum, The—: Its Structure and Function, Its Diseases and Their Medical and Surgical Treatment. E. L. KELLOGG. *Rev.* 137
- Duodenum, The Redundant—: Clinical Significance. T. H. MORRISON and M. FELDMAN 1126
- Dysinsulinism, Diabetes Mellitus, Hyperinsulinism and—; An Analytical Review of Data Relevant to the Classification and Terminology of the Secretory Disorders of the Is-

- lands of Langerhans of the Pancreas. Nomenclature of the Disorders of Insulin Secretion;— S. HARRIS 1084
- Dyspepsia, The Pernicious Type of Nervous— E. C. KLEIN, JR. 960
- E**DEMA, Management of— C. A. ELLIOTT 240
- Effect of Calcium on the Storage of Colloid in the Thyroid Gland, The— J. KLEIN 1080
- Effect of Hormones on Cellular Permeability, The— E. GELLHORN 33
- Effect of Pilocarpine on the Volume, Free and Combined Acid, Total Chlorides and Pepsin of Gastric Secretion, The—; And a Comparison with the Effects of Histamine Stimulation. L. J. MEIENBERG and C. L. BROWN ... 762
- Effect of Tobacco on Diseases of the Blood Vessels, The— *Edit.* 1456
- Effect of Vitamins and the Inorganic Elements on Growth and Resistance to Disease in Children, The— A. BROWN and F. F. TISDALL 342
- Electrocardiography, Multi-Plane Chest— A Standardized Method of Chest Lead Applications. J. WEINSTEIN.. 1503
- Electrocardiography, Research in— E. D. REID and S. H. CALDWELL 369
- Electropyrexia; A Résumé of Therapeutic Applications and Technics. S. OSBORNE and D. E. MARKSON 1391
- Encephalitis. *Edit.* 267
- Endocarditis, Subacute Bacterial— J. H. MUSSER 715
- Endocrine Glands in Bodily Adjustment, The— The Tides of Life. — R. G. HOSKINS. *Rev.* 406
- Endocrine Medicine. W. ENGELBACH. Volume I: General Considerations. Volume II: The Infantile Endocrinopathies. Volume III: The Adolescent Endocrinopathies. The Adult Endocrinopathies. Volume IV: Bibliography, Index. *Rev.* 407
- Endocrinology, Recent Advances in— A. T. CAMERON. *Rev.* 1332
- Entrance Requirements. *Edit.* 401
- Environment, Heredity and—; Studies in the Genesis of Psychological Characteristics. G. C. SCHWESINGER and F. OSBORN. *Rev.* 1560
- Epilepsy, The Evidence for a Cerebral Vascular Mechanism in— W. PENFIELD 303
- Ergotamine, Experimental and Clinical Studies of— V. The Action of Ergotamine on the Sympathetic Nervous System Stimulated by Epinephrine. Studies of the Metabolic Rate, Pulse Rate, Blood Pressure, Blood Sugar and the Total Leukocyte Count. J. B. YOUMANS, C. TRABUE and R. S. BUVINGER 653
- Etiology of Pernicious Anemia and Related Macrocytic Anemias, The— W. B. CASTLE 2
- Evaluation of Therapy in Chronic Atrophic Arthritis. W. P. HOLBROOK 457
- Evidence for a Cerebral Vascular Mechanism in Epilepsy, The— W. PENFIELD 303
- Exophthalmic Goiter, Hepatic Pathology in— C. V. WELLER 543
- Exophthalmic Goiter, The Pathologic Anatomy of the Liver in— D. C. BEAVER and J. DEJ. PEMBERTON 687
- Experimental and Clinical Studies in the Surgical Treatment of Angina Pectoris. J. C. WHITE 229
- Experimental and Clinical Studies of Ergotamine. V. The Action of Ergotamine on the Sympathetic Nervous System Stimulated by Epinephrine. Studies of the Metabolic Rate, Pulse Rate, Blood Pressure, Blood Sugar and the Total Leukocyte Count. J. B. YOUMANS, C. TRABUE and R. S. BUVINGER 653
- External Trauma in Relation to Ulcer of the Stomach and Duodenum. Report of Five Cases. I. GRAY 1403
- F**AMILIAL Factor in Hypochromic Anemia with Achlorhydria, The Hereditary and— W. H. BARROW 1135
- Familial Incidence of Peptic Ulcer, The— H. H. RIECKER 732
- Fat Metabolism, Aspects of Carbohydrate and— C. H. BEST 145
- Fatal Tularemia: Review of Autopsied Cases with Report of a Fatal Case. L. P. GUNDY and C. G. WARNER .. 837

- Federal Medical Care of the Unemployed. *Edit.* 669
- Felton's Serum, Recovery with—Pneumococcic Meningitis:— W. S. REVENO and N. McLAUGHLIN 1026
- Felty's Syndrome; Report of a Case with Complete Postmortem Findings. A. E. PRICE and J. B. SCHOENFELD. 1230
- Fragilitas Ossium in Five Generations. H. JOACHIM and M. G. WASCH 853
- Further Observations on the Treatment of Pernicious Anemia with Parenteral Horse Liver Extract; Including One Case of Pernicious Anemia Following Gastrectomy. O. RICHTER, A. E. MEYER and A. C. IVY 353
- Further Studies on the Pharmacology of Certain Phenol Esters with Special Reference to the Relation of Chemical Constitution and Physiologic Action. The Histopathology of Some Neurotoxic Phenol Esters. M. I. SMITH, E. W. ENGEL and E. F. STOHLMAN. *Rev.* 274
- G**ALACTOSURIA in the Diagnosis of Jaundice, The Value of Alimentary—. H. J. TUMEN and G. M. PIERSOL 311
- Gastric Acidity, The Clinical Significance of—. A Study of 6679 Cases with Digestive Symptoms. Z. SAGAL, J. A. MARKS and J. L. KANTOR ... 76
- Gastric Acidity, The Value of a Neutralization Test of—in Patients with Duodenal Ulcers and So-Called Pylorospasm. J. S. LEVY 1244
- Gastric Acidity, with the Report of a Case of Ulcerating Carcinoma in Which the—Changed from Normal to Anacidity while under Observation. A Consideration of the Gastric Ulcer-Cancer Problem;— H. SHAY and E. M. SCHLOSS 1218
- Gastric Anacidity. Its Relation to Disease. A. L. BLOOMFIELD and W. S. POLLAND. *Rev.* 272
- Gastric Ulcer-Cancer Problem, A Consideration of the—; with the Report of a Case of Ulcerating Carcinoma in Which the Gastric Acidity Changed from Normal to Anacidity while under Observation. H. SHAY and E. M. SCHLOSS 1218
- Gastro-Enterology, Modern Aspects of —. M. A. ARAFA. *Rev.* 409
- Gastrointestinal Allergy in Children. H. CASPARIS 625
- Glycine in the Treatment of Myasthenia Gravis, The Use of—. E. O. G. SCHMITT 948
- Glycosuria, Renal—. A. F. FOWLER .. 518
- Graphic Study of the Changes in the Muscular Activity of the Stomach Associated with Certain Epigastric Symptoms, A—. P. B. WELCH 251
- H**ANDBOOK of Chemotherapy. Part I. Metal Free Organic Compounds. V. FISCHL and H. SCHLOSSBERGER. *Rev.* 1459
- Handbook of Pulmonary Tuberculosis, A—. C. V. VISCHER and L. L. LANE. *Rev.* 272
- Heart, Diseases of the—. W. D. REID. *Rev.* 272
- Heart and the Surgeon, The—. *Edit.* 131
- Heart Block, Acquired—with Adams-Stokes Attacks Dependent upon a Congenital Anomaly (Persistent Ostium Primum); Report of a Case with Detailed Histopathologic Study. W. M. YATER, C. W. BARRIER and P. E. McNABB 1263
- Heart Block in the Young. I. I. LEMANN 779
- Heart Disease, The Cause of Death of Patients with Organic—Subjected to Surgical Operation. W. K. PURKS 885
- Heart Failure, Treatment of Angina Pectoris and Congestive—by Total Ablation of the Thyroid in Patients without Thyrotoxicosis. X. With Particular Reference to the Pre- and Postoperative Medical Management. H. L. BLUMGART, D. D. BERLIN, D. DAVIS, J. E. F. RISEMAN and A. A. WEINSTEIN 1469
- Hematological Diagnosis, Practical—. O. H. P. PEPPER and D. L. FARLEY. *Rev.* 273
- Hematological Response of Addisonian Pernicious Anemia to Brewer's Yeast. H. K. RUSSELL 1398
- Hepatic Complications in the Treatment of Syphilis; the Rose Bengal Test as a Means of Detecting Disturbances of Liver Function and Its Use as a

- Guide in the Therapy of Syphilis. G. R. BISKIND, N. N. EPSTEIN and W. J. KERR 966
- Hepatic Pathology in Exophthalmic Goiter. C. V. WELLER 543
- Hereditary and Familial Factor in Hypochromic Anemia with Achlorhydria, The—. W. H. BARROW 1135
- Heredity and Environment; Studies in the Genesis of Psychological Characteristics. G. C. SCHWESINGER and F. OSBORN. *Rev.* 1560
- Histamine Skin Test, A Painless—: An Experimental Study. S. PERLOW 561
- Histamine Stimulation, And a Comparison with the Effects of—. The Effect of Pilocarpine on the Volume, Free and Combined Acid, Total Chlorides and Pepsin of Gastric Secretion;—. L. J. MEIENBERG and C. L. BROWN 762
- History of Urology. Volumes I and II. B. LEWIS, E. G. BALLENGER, W. A. FRONTZ and H. G. HAMER. *Rev.* 792
- Hormones, Differentiating Some Functions of the Anterior Pituitary—. O. RIDDLE 23
- Hormones and Menstrual Disorders, Concerning Placental—. A. D. CAMPBELL 330
- Hormones on Cellular Permeability, The Effect of—. E. GELLHORN 33
- Hospital Medical Statistics. C. R. MARTIN. *Rev.* 1333
- Hospitals, American and Canadian—. J. C. FIFIELD. *Rev.* 275
- Human Constitution: A Study of the Correlations between Physical Aspects of the Body and Susceptibility to Certain Diseases. W. FREEMAN 805
- Human Sex Anatomy. R. L. DICKINSON. *Rev.* 1560
- Hygiene of the Mind. BARON E. VON FEUCHTERSLEBEN. *Rev.* 1053
- Hyperinsulinism, Hypoglycemia and—. M. K. TEDSTROM 1013
- Hyperinsulinism and Dysinsulinism, Diabetes Mellitus,—; An Analytical Review of Data Relevant to the Classification and Terminology of the Secretory Disorders of the Islands of Langerhans of the Pancreas. Nomenclature of the Disorders of Insulin Secretion;—. S. HARRIS 1084
- Hypersensitiveness to the Emanations of the Caddis Fly (*Trichoptera*), Studies of—. V. A. Report of Its Distribution. S. J. PARLATO, P. J. LADUCA and O. C. DURHAM 1420
- Hypertension, Paroxysmal—. *Edit.* ... 530
- Hypertension, The Parenteral Administration of Magnesium Sulphate in—. B. L. ZOHMAN and B. STERNBERG 643
- Hypertension among Urban Japanese, The Incidence of—. H. HASHIMOTO, K. AKATSUKA, I. TSUJII and H. SHIRAISHI 615
- Hyperthyroidism, Irradiation Treatment of—. G. E. PFAHLER 868
- Hypoglycemia and Hyperinsulinism. M. K. TEDSTROM 1013
- Hypothyroidism, Mild—. R. M. WATKINS 1534
- I**MPORTANCE of Bronchoscopy in Bronchiectasis, The—. H. P. MARVIN 903
- Incidence and Significance of the Sickle Cell Trait, The—. L. W. DIGGS, C. F. AHMANN and J. BIBB 769
- Incidence of Hypertension among Urban Japanese, The—. H. HASHIMOTO, K. AKATSUKA, I. TSUJII and H. SHIRAISHI 615
- Index of Prognosis and End-Results of Treatment, An—. A. R. SHORT, Editor. *Rev.* 678
- Index of Treatment, An—. R. HUTCHINSON, Editor. *Rev.* 677
- Indications for Collapse Therapy in Pulmonary Tuberculosis, The—. I. D. BRONFIN 468
- Indigestion, The Common Causes of Chronic—. Differential Diagnosis and Treatment. T. C. HUNT. *Rev.* 273
- Infection, The Rôle of Desensitization in Recovery from Bacterial—. W. B. WHERRY 728
- Influence of the Adrenal Cortex upon Salt and Water Metabolism, The—. *Edit.* 402
- Insulin Secretion, Nomenclature of the Disorders of—: Diabetes Mellitus, Hyperinsulinism and Dysinsulinism; An Analytical Review of Data Relevant to the Classification and Terminology of the Secretory Disorders

- of the Islands of Langerhans of the Pancreas. S. HARRIS 1084
- Internist as His Own Psychiatrist, The—. A STENGEL 281
- Interpretation of Dreams, The—. S. FREUD. *Rev.* 1052
- Intravenous Vaccine Therapy in Chronic Arthritis. W. B. RAWLS, B. J. GRUSKIN and A. RESSA 566
- Iodine, The Diagnostic Use of—in Thyrotoxicosis. J. H. MEANS 439
- Irradiation Treatment of Hyperthyroidism. G. E. PFAHLER 868
- J**AUNDICE, The Analgesic Effect of Hepatitis and—in Chronic Arthritis, Fibrositis and Sciatic Pain. P. S. HENCH 1278
- Jaundice, The Value of Alimentary Galactosuria in the Diagnosis of—. H. J. TUMEN and G. M. PIERSOL .. 311
- Jejunum, Primary Carcinoma in the—. Report of Two Unusual Cases of Primary Carcinoma: I. Primary Carcinoma in the Liver, with Cirrhosis of the Liver, Occurring in a Female. II.—. R. FINKELSTEIN and M. JACOBI 1319
- John Phillips Memorial Prize, Presentation of—to Dr. William Castle. F. M. POTTENGER 1
- Justification of the Diagnosis of Chronic Nervous Exhaustion, A—. J. W. MACY and E. V. ALLEN 861
- K**AHN Test, The Clinical Value of the Presumptive—. T. CAJIGAS 114
- L**IFE in the Making. A. F. GUTTMACHER and E. RAND. *Rev.* 791
- Liver, The Pathologic Anatomy of the—in Exophthalmic Goiter. D. C. BEAVER and J. DEJ. PEMBERTON 687
- Liver and Spleen, The Differential Diagnosis of Diseases of the—with the Aid of Roentgenography after the Intravenous Injection of Thorium Dioxide Sol (Thorotrast): Experience with Eighty Patients. W. M. YATER and L. S. OTELL 381
- Liver Function, The Rose Bengal Test as a Means of Detecting Disturbances of—and Its Use as a Guide in the Therapy of Syphilis. Hepatic Complications in the Treatment of Syphilis;—. G. R. BISKIND, N. N. EPSTEIN and W. J. KERR 966
- Localization of Disease in the Body, Some Factors in the—. H. BURROWS. *Rev.* 536
- Lung, The Rheumatic—. C. P. HOWARD 165
- Lungs, Congenital Cystic Disease of the—. Case Reports. L. J. MOORMAN 1523
- Lymphedema, A Case of Persistent—Involving the Left Arm, Left Face, and Left Thorax. R. GURNEY and F. HUBER 1431
- Lyophilic Colloids, The—(Their Theory and Practice). M. H. FISCHER and M. O. HOOKER. *Rev.* 1151
- M**ACROCYTIC Anemias, The Etiology of Pernicious Anemia and Related—. W. B. CASTLE 2
- Management of Edema. C. A. ELLIOTT 240
- Malaria Therapy in Asymptomatic Neurosyphilis. P. A. O'LEARY 1513
- Malaria Treatment of Parenchymatous Syphilis of the Central Nervous System. R. A. VONDERLEHR. *Rev.* ... 1052
- Medical Secretary, The—. M. G. MORSE. *Rev.* 138
- Medicine. Der Dialektische Materialismus und die klinische Medizin. J. LIFSCHITZ. *Rev.* 680
- Medicine, A System of Clinical—. T. D. SAVILL. *Rev.* 1461
- Medicine, Chinese—. (Clio Medica.) W. R. MORSE. E. B. KRUMBHAR, Editor. *Rev.* 1460
- Medicine, Psychiatric Investigation in Internal—. M. L. CARNS and A. C. WASHBURN 664
- Medicine, Psychoanalysis and—. A Study of the Wish to Fall Ill. K. STEPHEN. *Rev.* 792
- Medicine, The Source of Modern—. An Address to the American College of Physicians. Sir A. MACPHAIL . 120
- Medicine and Surgery, The Practitioner's Library of—. G. BLUMER, Supervising Editor. Volume IV: Nontraumatic Surgery. T. S. MOISE, JR., Associate Editor. *Rev.* 407
- Medicine and Surgery, The Practitioner's Library of—. G. BLUMER, Supervising Editor. Volume V: Trau-

- matic Surgery. T. S. MOÏSE, JR., Associate Editor. Volume VI: Obstetrics and Gynecology. L. K. MUSSELMAN, Associate Editor. *Rev.* 1458
- Meningitis, Pneumococcic—: Recovery with Felton's Serum. W. S. REVENO and N. McLAUGHLIN 1026
- Menstrual Disorders, Concerning Placental Hormones and—. A. D. CAMPBELL 330
- Mental Deficiency Due to Birth Injuries. E. H. DOLL, W. M. PHELPS and R. T. MELCHER. *Rev.* 794
- Mental Hygiene, Studies in—. Adolescence:—. F. E. WILLIAMS. *Rev.* 793
- Mental Hygiene in the Community. C. BASSETT. *Rev.* 1150
- Metabolic Diseases and Their Treatment. E. GRAFE. *Rev.* 1149
- Methylene Blue, Toxicology and Assay of—. D. I. MACHT and W. C. HARDEN 738
- Mind, Hygiene of the—. BARON E. VON FEUCHTERSLEBEN. *Rev.* 1053
- Modern Treatment of Syphilis, The—. J. E. MOORE. *Rev.* 1331
- Mortality Rate in Ukrania, The—. *Edit.* 532
- Mouth, Diseases of the—. S. V. MEAD. *Rev.* 535
- Mucin in the Treatment of Peptic Ulcer Associated with Renal and Hepatic Disease. A. B. RIVERS and F. R. VANZANT 1122
- Multi-Plane Chest Electrocardiography. A Standardized Method of Chest Lead Applications. J. WEINSTEIN .. 1503
- Myasthenia Gravis, The Use of Glycine in the Treatment of—. E. O. G. SCHMITT 948
- Myeloid Insufficiency. R. GOTTLIEB ... 895
- Myxedema, Chronic Pericardial Effusion in—: Report of Case. E. B. FREEMAN 1070
- N**ERVOUS Breakdown. W. B. WOLFE. *Rev.* 534
- Nervous Exhaustion, A Justification of the Diagnosis of Chronic—. J. W. MACY and E. V. ALLEN 861
- Neurology. R. R. GRINKER. *Rev.* ... 1458
- Neurosyphilis, Malaria Therapy in Asymptomatic—. P. A. O'LEARY .. 1513
- Neurosyphilis, Ultrahigh Frequency Pyretotherapy of—. A Preliminary Report. W. M. SIMPSON, F. K. KISLIG and E. C. SITTLER 64
- Nomenclature of the Disorders of Insulin Secretion: Diabetes Mellitus, Hyperinsulinism and Dysinsulinism; An Analytical Review of Data Relevant to the Classification and Terminology of the Secretory Disorders of the Islands of Langerhans of the Pancreas. S. HARRIS 1084
- Nutrition. G. LUSK. *Clio Medica: A Series of Primers on the History of Medicine.* E. B. KRUMBHAAR, Editor. Volume X. —. *Rev.* 916
- O**BITUARIES:
- Adams, Samuel Franklin 797
- Barnes, Noble Price 922
- Bathurst, William Ray 798
- Bringhurst, Joseph 1468
- Dunn, Arthur D. 1199
- Eckel, George J. 1057
- Grayson, Thomas Wray 416
- Grigg, Adrian Hansford 1058
- Harding, George T., Jr. 1341
- Harris, Raymond Joseph 540
- Hoff, Albert Ewalt 1342
- Hunter, George 1198
- Johnson, Frank Chambliss 1341
- Keyes, Frank Perkins 921
- Lappeus, John C. S. 921
- Loucks, Roland E. 414
- McClymonds, Julian Turnbull 1198
- McKean, George E. 1343
- McKinney, Thomas Jefferson 280
- McNabb, Paul Edgar 1339
- Mercur, William Henry 413
- Morris, Roger Sylvester 1338
- Otis, Edward Osgood 539
- Shellito, Judd Campbell 415
- Stallings, Walker Eugene 143
- Stewart, William Blair 279
- van Valzah, Shannon Laurie 540
- Wolfe, John Bloss 142
- Obliterating Thrombosis of the Pulmonary Arteries. W. M. FOWLER .. 1101
- Observations of a General Practitioner. W. N. MACARTNEY. *Rev.* 1333
- Old Age, Diseases of—. F. M. LIPSCOMB. *Rev.* 1054
- Osteitis Deformans. A Review of the Literature and Report of Eleven Cases. J. W. KERR. *Rev.* 791

- Osteomalacia, The Significance of the Hypertrophy and Hyperplasia of the Parathyroid Glands in Rickets and —. R. M. WILDER, G. M. HIGGINS and C. SHEARD 1059
- Oxygen Deprivation (Anoxemia) on Human Behavior, The Psychological Effects of—. R. C. MCFARLAND. *Rev.* 917
- P**AINLESS Histamine Skin Test, A —: An Experimental Study. S. PERLOW 561
- Parathyroid Glands in Rickets and Osteomalacia, The Significance of the Hypertrophy and Hyperplasia of the —. R. M. WILDER, G. M. HIGGINS and C. SHEARD 1059
- Parenteral Administration of Magnesium Sulphate in Hypertension, The —. B. L. ZOHMAN and B. STERNBERG 643
- Parenteral Liver Therapy in Pernicious Anemia: Observations Covering Two Years of Continued Use. J. E. CONNERY and L. J. GOLDWATER 1117
- Paroxysmal Hypertension. *Edit.* 530
- Paroxysmal Ventricular Tachycardia: An Etiological Study with Special Reference to the Type. C. J. LUNDY and L. L. McLELLAN 812
- Pathologic Anatomy of the Liver in Exophthalmic Goiter, The—. D. C. BEAVER and J. DEJ. PEMBERTON 687
- Pediatrics. H. D. CHAPIN and L. T. ROYSTER. *Rev.* 679
- Peptic Ulcer. J. BUCKSTEIN. *Rev.* .. 137
- Peptic Ulcer, Mucin in the Treatment of—Associated with Renal and Hepatic Disease. A. B. RIVERS and F. R. VANZANT 1122
- Peptic Ulcer, The Familial Incidence of—. H. H. RIECKER 732
- Periarteritis Nodosa. A Brief Review of the Literature and Report of One Case. A. C. CURTIS and R. M. COFFEY 1345
- Pericardial Effusion in Myxedema, Chronic—: Report of Case. E. B. FREEMAN 1070
- Pericardial Metastasis, Clinical Aspects of—. B. R. HENINGER 1359
- Pernicious Anemia, Further Observations on the Treatment of—with Parenteral Horse Liver Extract; Including One Case of Pernicious Anemia Following Gastrectomy. O. RICHTER, A. E. MEYER and A. C. IVY 353
- Pernicious Anemia, Hematological Response of Addisonian—to Brewer's Yeast. H. K. RUSSELL 1398
- Pernicious Anemia, Parenteral Liver Therapy in—: Observations Covering Two Years of Continued Use. J. E. CONNERY and L. J. GOLDWATER 1117
- Pernicious Anemia and Lesions of the Gastrointestinal Tract, Coexistence of—. I. Carcinoma of the Stomach. Consideration of Twenty Cases: Eleven Reported. H. M. CONNER and I. W. BIRKELAND 89
- Pernicious Anemia and Related Macrocytic Anemias, The Etiology of—. W. B. CASTLE 2
- Pernicious Type of Nervous Dyspepsia, The—. E. C. KLEIN, JR. 960
- Personality, Diet and—. Fitting Food to Type and Environment. L. J. BOGERT. *Rev.* 1152
- Pharmacology of Certain Phenol Esters, Further Studies on the—with Special Reference to the Relation of Chemical Constitution and Physiologic Action. The Histopathology of Some Neurotoxic Phenol Esters. M. I. SMITH, E. W. ENGEL and E. F. STOHLMAN. *Rev.* 274
- Phenol Esters, Further Studies on the Pharmacology of Certain—with Special Reference to the Relation of Chemical Constitution and Physiologic Action. The Histopathology of Some Neurotoxic Phenol Esters. M. I. SMITH, E. W. ENGEL and E. F. STOHLMAN. *Rev.* 274
- Phyloanalysis: a Study in the Group of Phyletic Method of Behavior-Analysis. W. GALT. *Rev.* 1561
- Physical Chemistry of Living Tissues and Life Processes. R. BEUTNER. *Rev.* 138
- Pilocarpine, The Effect of—on the Volume, Free and Combined Acid, Total Chlorides and Pepsin of Gastric Secretion; And a Comparison with the Effects of Histamine Stimulation. L. J. MEIENBERG and C. L. BROWN .. 762

- Pituitary Hormones, Differentiating Some Functions of the Anterior—. O. RIDDLE 23
- Pleura, Calcification of the—. J. HEAD 1295
- Pneumococcic Meningitis: Recovery with Felton's Serum. W. S. REVENO and N. McLAUGHLIN 1026
- Pneumonia, Tularemic—. P. G. BOMAN and A. J. BIANCO 1491
- Pollen Extracts, The Treatment of Chronic Intractable Asthma with—. G. L. WALDBOTT 508
- Polycythemia, Treatment of—. The Reticulocyte Response to Venesection, Phenylhydrazin and Radiation. E. H. FALCONER 172
- Polycythemia in Association with Pulmonary Disorders. J. J. WARING and W. B. YEGGE 190
- Practical Hematological Diagnosis. O. H. P. PEPPER and D. L. FARLEY. *Rev.* 273
- Practitioner, Observations of a General —. W. N. MACARTNEY. *Rev.* 1333
- Practitioner's Library of Medicine and Surgery. G. BLUMER, Supervising Editor. Volume IV: Nontraumatic Surgery. T. S. MOISE, JR., Associate Editor. *Rev.* 407
- Practitioner's Library of Medicine and Surgery, The—. G. BLUMER, Supervising Editor. Volume V: Traumatic Surgery. T. S. MOISE, JR., Associate Editor. Volume VI: Obstetrics and Gynecology. L. K. MUSSELMAN, Associate Editor. *Rev.* 1458
- Presentation of the John Phillips Memorial Prize to Dr. William Castle. F. M. POTTENGER 1
- Primum Non Nocere. *Edit.* 1327
- Problems of Pulmonary Tuberculosis in General Practice. R. FITZ 245
- Prognosis and End-Results of Treatment, An Index of—. A. R. SHORT, Editor. *Rev.* 678
- Progress or Retrogress. *Edit.* 1048
- Psychiatric Investigation in Internal Medicine. M. L. CARNS and A. C. WASHBURNE 664
- Psychiatrist, The Internist as His Own —. A. STENGEL 281
- Psychoanalysis. *Edit.* 1146
- Psychoanalysis, New Introductory Lectures on—. S. FREUD. *Rev.* 1052
- Psychoanalysis and Medicine. A Study of the Wish to Fall Ill. K. STEPHEN. *Rev.* 792
- Psychological Effects of Oxygen Deprivation (Anoxemia) on Human Behavior, The—. R. C. McFARLAND. *Rev.* 917
- Psychopathology of Crime, Case Studies in the—. B. KARPMAN. *Rev.* 405
- Pure Food and Drug Bill, The New—. *Edit.* 1048
- Pylorospasm, The Value of a Neutralization Test of Gastric Acidity in Patients with Duodenal Ulcers and So-Called—. J. S. LEVY 1244
- Pyretotherapy of Neurosyphilis, Ultrahigh Frequency—. A Preliminary Report. W. M. SIMPSON, F. K. KISLIG and E. C. SITTLER 64
- R**ADIOLOGIC Maxims. H. SWANBERG. *Rev.* 1052
- Rational Treatment of the Anemic Patient. W. P. MURPHY 939
- Rectum, and Anus, The Colon—. F. W. RANKIN, J. A. BARGEN and L. A. BUIE. *Rev.* 917
- Redundant Duodenum; The—: Clinical Significance. T. H. MORRISON and M. FELDMAN 1126
- Relationship of Sex to Disease, The—. E. V. ALLEN 1000
- Relationship of the Autonomic Nervous System to General Medicine, The—. T. P. SPRUNT 257
- Renal Glycosuria. A. F. FOWLER 518
- Renal Insufficiency Following Blood Transfusion; Recovery after Venesection. H. T. VONDEESTEN and S. A. COSGROVE 105
- Report of a Case of Diverticulosis of the Small Intestine with a Critical Review of Recent Literature. J. CHAPMAN 1376
- Report of Two Unusual Cases of Primary Carcinoma: I. Primary Carcinoma in the Liver, with Cirrhosis of the Liver, Occurring in a Female. II. Primary Carcinoma in the Jejunum. R. FINKELSTEIN and M. JACOBI 1319
- Research in Electrocardiography. W. D. REID and S. H. CALDWELL 369
- Rheumatic Lung, The—. C. P. HOWARD 165

- Rickets and Osteomalacia, The Significance of the Hypertrophy and Hyperplasia of the Parathyroid Glands in—. R. M. WILDER, G. M. HIGGINS and C. SHEARD 1059
- Rôle of Desensitization in Recovery from Bacterial Infection, The—. W. B. WHERRY 728
- Röntgen, Wilhelm Conrad—and the Early History of the Roentgen-Rays. O. GLASSER. *Rev.* 1460
- S**ANGRE IMPURA in Mora; A Study of Syphilis and Certain Other Diseases in the Population of Mora County, New Mexico. W. CLARKE . 1436
- Schizophrenia from the Physiological Point of View. R. G. HOSKINS 445
- Serum Therapy, Recent Advances in Vaccine and—. A. FLEMING and G. F. PETRIE. *Rev.* 1333
- Sex, The Relationship of—to Disease. E. V. ALLEN 1000
- Sex Anatomy, Human—. R. L. DICKINSON. *Rev.* 1560
- Shuckburgh, Dr. Richard—and Yankee Doodle. L. H. RODDIS 1548
- Sickle Cell Trait, The Incidence and Significance of the—. L. W. DIGGS, C. F. AHMANN and J. BIBB 769
- Significance of the Hypertrophy and Hyperplasia of the Parathyroid Glands in Rickets and Osteomalacia, The—. R. M. WILDER, G. M. HIGGINS and C. SHEARD 1059
- Sinus Infections and Colds, Diet in—. E. V. ULLMANN. *Rev.* 680
- Situs Inversus Viscerum Totalis in Siblings. Case Reports. E. A. GALL and V. F. WOOLF 1370
- Source of Modern Medicine, The—. An Address to the American College of Physicians. Sir A. MACPHAIL .. 120
- Spinal Cord, Anatomy of the Brain and—. W. W. LOONEY. *Rev.* 406
- Spinal Cord, Tuberculoma of the—. F. L. JENNINGS 1240
- Splanchnic Nerve Section in a Juvenile Diabetic, Bilateral—. G. DE TAKATS and G. K. FENN 422
- Splanchnic Nerve Section in Juvenile Diabetes. I. Selection of Cases for Operation. G. DE TAKATS, G. K. FENN and R. A. TRUMP 1201
- Spleen, The Differential Diagnosis of Diseases of the Liver. and—with the Aid of Roentgenography after the Intravenous Injection of Thorium Dioxide Sol (Thorotrast): Experience with Eighty Patients. W. M. YATER and L. S. OTELL 381
- Sporotrichosis; Report of a Case Originating in New York. G. M. LEWIS and J. H. CUDMORE 991
- Standard Test for Measuring the Variability of Blood Pressure, A—: Its Significance as an Index of the Prehypertensive State. E. A. HINES, JR. and G. E. BROWN 209
- Statistical Evaluation of Different Methods for the Detection of Arteriosclerosis in Diabetes Mellitus, A—. I. M. RABINOWITCH, W. L. RITCHIE and S. H. MCKEE 1478
- Statistics, Hospital Medical—. C. R. MARTIN. *Rev.* 1333
- Stewart, Dr. William Blair—. *Edit.* .. 266
- Stomach, A Graphic Study of the Changes in the Muscular Activity of the—Associated with Certain Epigastric Symptoms. P. B. WELCH .. 251
- Studies of Hypersensitiveness to the Emanations of the Caddis Fly (*Trichoptera*). V. A Report of Its Distribution. S. J. PARLATO, P. J. LA-DUCA and O. C. DURHAM 1420
- Studies on the Function and Clinical Use of Cortin. F. A. HARTMAN .. 6
- Subacute Bacterial Endocarditis. J. H. MUSSER 715
- Suicide, A Study of—. To Be or Not to Be. —. L. I. DUBLIN and B. BUNZEL. *Rev.* 793
- Surgery, The Practitioner's Library of Medicine and—. G. BLUMER, Supervising Editor. Volume IV: Non-traumatic Surgery. T. S. MOÏSE, JR., Associate Editor. *Rev.* 407
- Surgery, The Practitioner's Library of Medicine and—. G. BLUMER, Supervising Editor. Volume V: Traumatic Surgery. T. S. MOÏSE, JR., Associate Editor. Volume VI: Obstetrics and Gynecology. L. K. MUSSELMAN, Associate Editor. *Rev.* ... 1458
- Susceptibility to Certain Diseases, A Study of the Correlations between Physical Aspects of the Body and—.

- Human Constitution:— W. FREEMAN 805
- Syphilis, A Study of—and Certain Other Diseases in the Population of Mora County, New Mexico. *Sangre Impura* in Mora;— W. CLARKE .. 1436
- Syphilis, Hepatic Complications in the Treatment of—; The Rose Bengal Test as a Means of Detecting Disturbances of Liver Function and Its Use as a Guide in the Therapy of Syphilis. G. R. BISKIND, N. N. EPSTEIN and W. J. KERR 966
- Syphilis, The Modern Treatment of —. J. E. MOORE. *Rev.* 1331
- Syphilis of the Central Nervous System, Malaria Treatment of Parenchymatous—. R. A. VONDERLEHR. *Rev.* 1052
- Syphilitic Aortitis. *Edit.* 133
- System of Clinical Medicine, A—. T. D. SAVILL. *Rev.* 1461
- T**ACHYCARDIA, Paroxysmal Ventricular: An Etiological Study with Special Reference to the Type. C. J. LUNDY and L. L. McLELLAN 812
- Therapy, A New Approach to Dietetic—. E. FÖLDES. *Rev.* 535
- Thorium Dioxide Sol (Thorotrast), The Differential Diagnosis of Diseases of the Liver and Spleen with the Aid of Roentgenography after the Intravenous Injection of—: Experience with Eighty Patients. W. M. YATER and L. S. OTELL 381
- Thromboangiitis Obliterans of Patients with Diabetes. B. T. HORTON and F. N. ALLAN 799
- Thyroid Gland, The Effect of Calcium on the Storage of Colloid in the—. J. KLEIN 1080
- Thyroid in Patients without Thyrotoxicosis, Treatment of Angina Pectoris and Congestive Heart Failure by Total Ablation of the—. X. With Particular Reference to the Pre- and Postoperative Medical Management. H. L. BLUMGART, D. D. BERLIN, D. DAVIS, J. E. F. RISEMAN and A. A. WEINSTEIN 1469
- Thyrotoxicosis, The Diagnostic Use of Iodine in—. J. H. MEANS 439
- Tides of Life, The—. The Endocrine Glands in Bodily Adjustment. R. G. HOSKINS. *Rev.* 406
- To Be or Not to Be. A Study of Suicide. L. I. DUBLIN and B. BUNZEL. *Rev.* 793
- Tobacco, The Effect of—on Diseases of the Blood Vessels. *Edit.* 1456
- Toxicology and Assay of Methylene Blue. D. I. MACHT and W. C. HARDEN 738
- Treatment, An Index of—. R. HUTCHINSON, Editor. *Rev.* 677
- Treatment of Angina Pectoris and Congestive Heart Failure by Total Ablation of the Thyroid in Patients without Thyrotoxicosis. X. With Particular Reference to the Pre- and Postoperative Medical Management. H. L. BLUMGART, D. D. BERLIN, D. DAVIS, J. E. F. RISEMAN and A. A. WEINSTEIN 1469
- Treatment of Chronic Intractable Asthma with Pollen Extracts, The—. G. L. WALDBOTT 508
- Treatment of Circulatory Failure, The —. L. M. WARFIELD 981
- Treatment of Polycythemia. The Reticulocyte Response to Venesection, Phenylhydrazin and Radiation. E. H. FALCONER 172
- Tuberculoma of the Brain. M. LEWIS, E. B. FREILICH and O. B. RAGINS 1141
- Tuberculoma of the Spinal Cord. F. L. JENNINGS 1240
- Tuberculosis, A Handbook of Pulmonary—. C. V. VISCHER and L. L. LANE. *Rev.* 272
- Tuberculosis, Conservatism, the Key-note in the Treatment of—. C. H. COCKE 746
- Tuberculosis, The Indications for Collapse Therapy in Pulmonary—. I. D. BRONFIN 468
- Tuberculosis, Vitamin Therapy in Pulmonary—. IV. Comparison of the H-Ion Concentration of the Blood in Tuberculosis with Normals on the Same Dietary. P. D. CRIMM and H. L. WATSON 109
- Tuberculosis in General Practice, Problems of Pulmonary—. R. FITZ 245
- Tularemia, Fatal: Review of Autop-

- sied Cases with Report of a Fatal Case. L. P. GUNDRY and C. G. WARNER 837
- Tularemic Pneumonia. P. G. BOMAN and A. J. BIANCO 1491
- U**LCER, Peptic—. J. BUCKSTEIN. *Rev.* 137
- Ulcer of the Stomach and Duodenum, External Trauma in Relation to— Report of Five Cases. I. GRAY 1403
- Ultrahigh Frequency Pyretotherapy of Neurosyphilis. A Preliminary Report. W. M. SIMPSON, F. K. KISLIG and E. C. SITTLER 64
- Ultra-Violet Energy, Its Effect and Intensity at Various Locations and Altitudes. M. K. WYLDER, R. S. ROCKWOOD and S. B. LIPPINCOTT ... 605
- Undernutrition and Its Treatment by Adequate Diet. J. M. STRANG and F. A. EVANS 45
- Urine and Urinalysis. L. GERSHENFELD. *Rev.* 534
- Urology, History of—. Volumes I and II. B. LEWIS, E. G. BALLENGER, W. A. FRONTZ and H. G. HAMER. *Rev.* 792
- V**ACCINE and Serum Therapy, Recent Advances in—. A. FLEMING and G. F. PETRIE. *Rev.* 1333
- Vaccine Therapy, Intravenous—in Chronic Arthritis. W. B. RAWLS, B. J. GRUSKIN and A. RESSA 566
- Value of a Neutralization Test of Gastric Acidity in Patients with Duodenal Ulcers and So-Called Pylorospasm, The—. J. S. LEVY 1244
- Value of Alimentary Galactosuria in the Diagnosis of Jaundice, The—. H. J. TUMEN and G. M. PIERSOL .. 311
- Veins.* De Venarum Ostiolis, 1603, of Hieronymus Fabricius of Aquapendente (1533?-1619). Translated by E. J. FRANKLIN. *Rev.* 1050
- Vitamin Therapy in Pulmonary Tuberculosis. IV. Comparison of the H-Ion Concentration of the Blood in Tuberculosis with Normals on the Same Dietary. P. D. CRIMM and H. L. WATSON 109
- Vitamins, The Effect of—and the Inorganic Elements on Growth and Resistance to Disease in Children. A. BROWN and F. F. TISDALL 342
- W**ATER Metabolism, The Influence of the Adrenal Cortex upon Salt and—. *Edit.* 402
- Welch, William H. *Edit.* 1553
- X**ANTHOMA Accompanied by Hypercholesterolemia, Occurring in an Otherwise Normal Individual, and in an Individual with Acromegaly and Diabetes. T. H. MCGAVACK and H. C. SHEPARDSON 582
- Y**EAST, Hematological Response of Addisonian Pernicious Anemia to Brewer's—. H. K. RUSSELL 1398

NATIONAL POISON IVY ANTIGENS



The treatment of poison ivy (Rhus dermatitis) was entirely symptomatic and most unsatisfactory until the active antigen for specific treatment was produced.

Relief in a few hours and complete cure in a few days may be expected from Rhus Tox Antigen for poison ivy, Rhus Venenata Antigen for poison oak.

These Antigens are prepared under U. S. Government License No. 102 and are accepted by The Council of The A. M. A. Reprint from articles published in Jour. A. M. A.; Med. Jour. and Rec.; Arch. of Dermatology mailed on request.

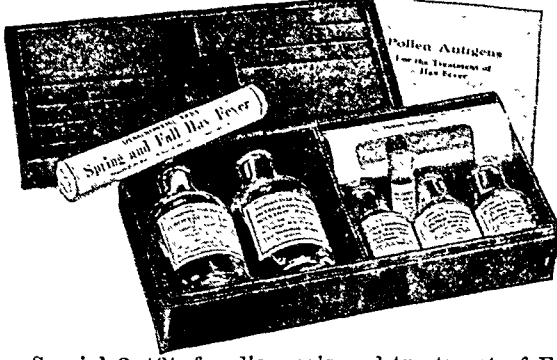
The Antigens retain their potency for at least three years; furnished in packages containing four 1 cc. Ampul-Vials. Physicians price \$3.50.

2—1 cc. syringes, (with rustless steel needles) \$2.25

Ragweed Antigen for Treatment of Fall Hay Fever

Complete Treatment (24 doses) in 5 cc. Ampul-vials

V 209	{ Series "AA" 125 nitrogen units (8 doses)	\$3.50
	{ Series "A" 250 nitrogen units (8 doses)	
	{ Series "B" 500 nitrogen units (8 doses)	



We offer the above Special Outfit, for diagnosis and treatment of Fall Hay Fever, containing two diagnostic tests, 1 ampul-vial each of Series "AA," "A" and "B" Ragweed Antigen; 25 cc. ampul-vial of Sterile Salt Solution, for dilution of Antigen if needed; 25 cc. ampul-vial of Epinephrin 1-1000, to control local or systemic reactions.

V 216 Ragweed Antigen Outfit complete, \$10.00

THE NATIONAL DRUG COMPANY
PHILADELPHIA
U.S.A.



Mail Hay Fever and Poison Ivy Antigen Brochures per Annals of Internal Medicine.

NameDate.....

Address

PRACTICE FOR SALE

SCHENECTADY, N. Y.

Thirty-three year practice of a deceased Fellow of the American College of Physicians — General practitioner, pathologist and bacteriologist. Private laboratory and office in home; complete equipment; eleven room house, centrally located, for rent or sale.

MRS. OTTOLINE B. STONE

415 Union St.
Schenectady, N. Y.

Your Patients on Low Carbohydrate Diets Will Appreciate

CURDOLAC FOODS

Curdolac Breakfast Cereal
Curdolac Soya Flour
Curdolac Wheat-Soya Flour
Curdolac Soya Cereal Johnny Cake Flour
Curdolac Soya-Bran Breakfast Food
Curdolac Soya-Bran Flour
Cakes, Cookies

•
*Palatable—Nutritious
Satisfying*
•

Samples and Literature
on Request

CURDOLAC FOOD CO.
Box 299 - - Waukesha, Wis.

PROFESSIONAL PROTECTION



THERE IS
NO SUBSTITUTE
FOR
EXPERIENCE

THE
MEDICAL PROTECTIVE COMPANY
OF FORT MYER, INDIANA
WHARTON, ILLINOIS

Fellowship Key



A charm, bearing the seal of The American College of Physicians; wrought in solid gold and embossed in The College colors. For Fellows only.

Price, \$7.00, postpaid

Available also in pin with safety catch.

Price, \$4.00, postpaid

Send orders to

E. R. Loveland, Executive Secretary
The American College of Physicians
133-135 S. 36th Street
Philadelphia, Pa.



TRADE **PYRIDIUM** MARK

PHENYLAZO-ALPHA-ALPHA-DIAMINO-PYRIDINE MONO-HYDROCHLORIDE. MFD. BY PYRIDIUM CORP., N. Y.

"Good afternoon doctor...are you prescribing Pyridium?"

IN CASE you have never given Pyridium a trial, may we suggest that you do not delay further in taking advantage of its usefulness. It is very valuable for the alleviation of the distressing symptoms that often accompany genito-urinary infections, as well as in the treatment of these infections.



MERCK & CO. INC. • Rahway, N. J.
MANUFACTURING CHEMISTS

The WYATT CLINIC

for

Chronic Arthritis



TUCSON, ARIZONA

HARVARD MEDICAL SCHOOL COURSES FOR GRADUATES

CARDIOLOGY

August 1-31

ADVANCED CARDIOLOGY

September 1-30

Both courses are given by Dr. Paul D. White, Dr. Howard B. Sprague and associates, at the Massachusetts General Hospital, six mornings and four afternoons a week. Attendance limited to 16. Women are admitted.

Fee, \$150 per course

For information write Assistant
Dean, Courses for Graduates

HARVARD MEDICAL SCHOOL,
Boston, Massachusetts

The Potts Memorial Hospital, Inc.

Livingston, Columbia Co., New York

One hundred miles north of
New York City.

Forty miles south of Albany.

Private rooms for the reception of patients who have undergone phrenicectomy, artificial pneumothorax, or thoracoplasty; also minimal and moderately advanced cases of tuberculosis needing bed care. Rate \$25.00 per week.

There are openings, from time to time, for quiescent and arrested cases of tuberculosis who need rehabilitation treatment. Graduated work, under medical supervision, in Printing, Gardening, Poultry Raising, Nursing, Clerical and Domestic work for men and women between the ages of eighteen and fifty. Pleasant surroundings and the best of care make this an ideal place to complete the cure. Descriptive brochure, giving rates, will be sent upon request.

H. A. PATTISON, M.D., *Director*
L. M. NIESEN, M.D.,
Resident Physician

Hospital Consultation and Advisory Service

THE voluntary prepayment method of meeting unpredictable hospital costs, conducted on a non-profit basis, has received the endorsement of numerous State and County Medical Societies. Advantages to patients, hospitals and doctors have attended all equitable, ethical plans thus far undertaken. Sound advice and guidance are helpful in launching such a project.

Office of
WILLIAM HENRY WALSH, M.D.
612 North Michigan Avenue
CHICAGO

The Desert Sanatorium

Altitude 2,600

Tucson, Arizona

Allen K. Krause

Director

This standard institution will be open and operating in all departments during the present summer.

Especially recommended for chronic nontuberculous focal pulmonary conditions, asthma, recurrent rheumatic fever and hypertension, chronic arthritis, the anaemias, etc., during the heated season.

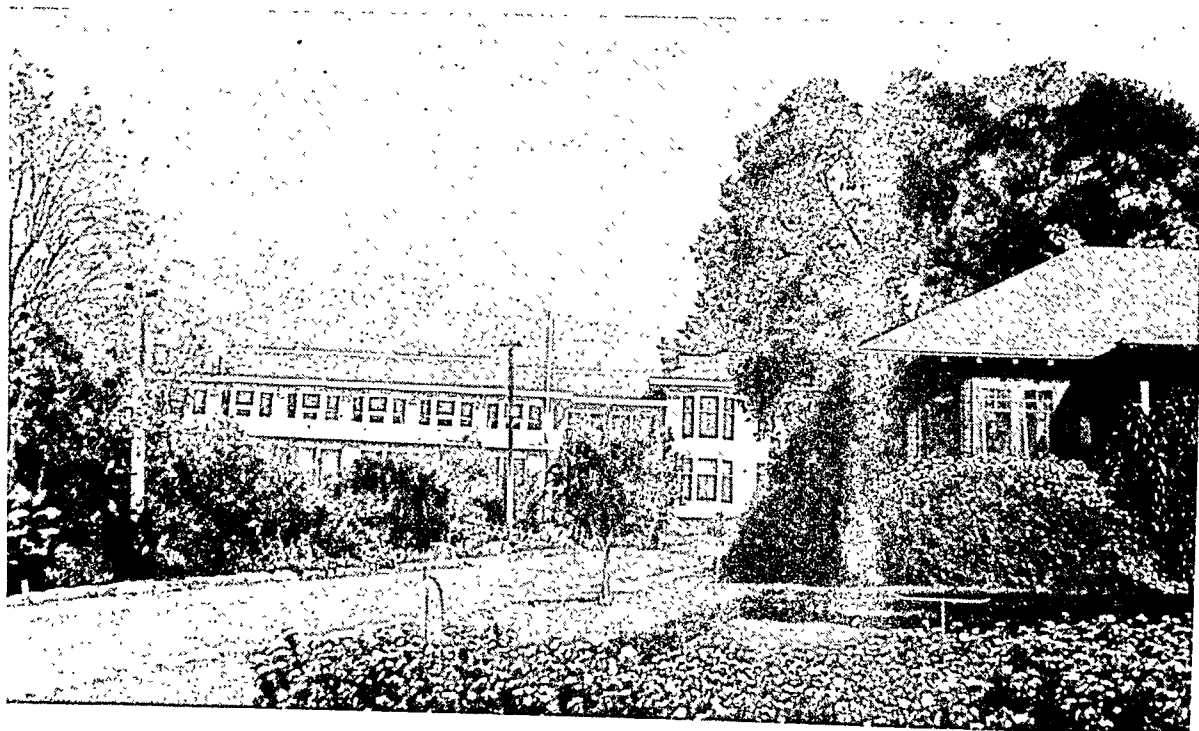
Tuberculosis of all forms accepted as outpatients during the summer. Nights generally cool and recuperative.

Splendidly equipped and staffed outpatient Clinic for patients in residence outside. Most convenient and attractive quarters for inpatients.

Write for booklet and rates

THE POTTENGER SANATORIUM AND CLINIC FOR DISEASES OF THE CHEST

Monrovia, California



THIRTY YEARS' EXPERIENCE IN THE TREATMENT OF TUBERCULOSIS

LOCATION

Sixteen miles east of Los Angeles. In the foothills of the Sierra Madre Mountains, at an elevation of 1000 feet. On the main line of Santa Fe Railway. Connected with Los Angeles by interurban railway and splendid boulevards.

ENVIRONS

The grounds consist of a beautiful park of forty acres, in which are found a variety of native Live Oaks, subtropical trees and plants, and a profusion of beautiful shrubs and flowers. Many winding walks and nooks of exquisite beauty add to its attractiveness. When on exercise, patients also enjoy the beautiful trails in the adjoining canyons and mountains.

MEDICAL CARE

Competent resident staff. Examinations for comparison every six weeks. Close medical supervision. Individual needs and problems receive personal attention.

THERAPEUTIC CARE

Fads are not followed, but an endeavor is made to give patients the amount of rest and exercise suited to their individual needs; the benefits of a liberal and adequate diet; such tonic measures as will increase their resistance, and other measures that will help them overcome any disturbing symptoms or complications that may arise. Heliotherapy, tuberculin, pneumo-thorax and surgery employed whenever indicated.

Weekly rates from \$25.00 up, including medical attention, medicines (except expensive remedies) and general nursing. Extra charge for operative measures (except pneumothorax).

DIAGNOSTIC CLINIC

A diagnostic clinic is maintained for the study of all diseases of the chest.

F. M. POTTENGER, M.D., Medical Director

For Particulars Address

THE POTTENGER SANATORIUM, Monrovia, California

Please Mention this Journal when writing to Advertisers

THE ANALYSIS SHOWS

THE VALUABLE ALKALINE CHARACTER OF

VICHY CÉLESTINS

Natural Mineral Water

INDICATIONS

In stomach and
liver affections
and digestive disorders
in general;
in gout, arthritis
associated with uric
acidemia, uricemia,
and nephrolithiasis of
uric acid origin.



BOTTLED
AT THE SPRING
VICHY, FRANCE

ANALYSIS (GRAMS PER LITER)

Sodium bicarbonate	3.3090
Potassium bicarbonate	0.2490
Lithium bicarbonate	0.0281
Calcium bicarbonate	0.7400
Magnesium bicarbonate	0.1016
Ferrous bicarbonate	0.0012
Sodium chloride	0.3830
Sodium sulphate	0.2430
Silica	0.0300
Sodium arseniate, Phosphate and nitrate	} present

Brochure with Therapeutic Data and Medical Bibliography
sent on request.

Sole United States Agents, American Agency of French Vichy, Inc., 503 Fifth Ave., New York